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Ambient Water Quality Criteria: Selenium

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SELENIUM

Ambient Water Quality Criteria

Criteria and Standards Division
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CRITERION DOCUMENT

SELENIUM

Criteria

Aquatic Life

For selenium the criterion to protect freshwater aquatic life, as derived using procedures other than the Guidelines, is 9.7 µg/l as a 24-hour average and the concentration should never exceed 22 µg/l at any time.

For selenium the criterion to protect saltwater aquatic life as derived using the Guidelines is 4.4 µg/l as a 24-hour average and the concentration should not exceed 10 µg/l at any time.

Human Health

For the protection of human health from the toxic properties of selenium ingested through water and through contaminated aquatic organisms, the ambient water criterion is determined to be 10 µg/l.

BIBLIOGRAPHIC INFORMATION

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for selenium. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no , ...

KEYWORDS: *Water quality, *Toxicology, *Selenium, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances, *Water pollution effects(Plants).

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Introduction

Selenium is a naturally occurring element used in photocopying, the manufacture of glass, electronic devices, pigments, dyes and insecticides (Dep. Inter. 1974). It is also used in veterinary medicine (Windholz, 1976) and antidandruff shampoos (Cummins and Kimura, 1971). The major source of selenium in the environment is the weathering of rocks and soils (Rosenfeld and Beath, 1964) but human activities contribute about 3,500 metric tons per year (U.S. EPA, 1975).

Selenium reacts with metals to form ionic selenides with a valence of minus 2 and with most other chemicals to form covalent compounds. It may assume any of several valence states ranging from minus 2 to plus 6. Depending on its oxidation state, selenium may act as either an oxidizing agent or a reducing agent (National Academy of Sciences, 1976). Inorganic selenium may be converted to organic forms by biological action (National Academy of Sciences, 1976). Biological systems may also convert non-volatile selenium compounds to volatile ones which might escape to air (Chan, et al. 1976).

Solubilities of selenium compounds range from very high (e.g., greater than 40 percent by weight for sodium selenate) to very low (e.g., 16,000 to 33,000 µg/l for the silver selenates) (Chizhikov and Schastlivyi, 1968). Heavy metal selenides are very insoluble (National Academy of Sciences, 1976).

Selenium is acutely toxic to aquatic invertebrates and to fishes.

Normal human selenium intake has been estimated at 50 to 150 µg per day (Sakurai and Tsuchiya, 1975). While selenium is an essential nutrient for humans and other species (Schroeder, 1974) it is toxic in excessive amounts (Halverson, et al. 1966; Rosenfeld and Beath, 1954). Selenium poisoning produces symptoms in man similar to those of arsenic (Keboe, et al. 1944; Fairhill, 1941). It has been shown to produce tumors in animals (Nelson, et al. 1943; Innes, et al. 1969) and is among the list of cancer-producing agents prohibited by the Delaney Clause (Schroeder, 1974).

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

The published data base on the effects of selenium on freshwater organisms is limited and there are no data on the chronic effects other than mortality to fish or invertebrate species. However, these data do indicate that there is a large difference between 96-hour LC50 values and 48- to 96-day LC50 values. Selenium does not bioconcentrate to a great extent and the data indicate that tissue residues should not be a hazard to freshwater organisms.

Acute Toxicity

Cardwell, et al. (1976) exposed six fish species to selenium dioxide using flow-through procedures and measured concentrations. The 96-hour LC50 values ranged from 2,060 to 28,500 µg/l (Table 1), and represent an order of magnitude variation in sensitivity. Most species were tested as juveniles and this sensitivity range is probably not appreciably affected by the life stage. The 96-hour LC50 values for fathead minnow fry and juveniles are 2,060 and 5,200 µg/l, respectively which indicates an apparent decrease in toxicity with age.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

The geometric mean LC50 divided by the Guidelines sensitivity factor of 3.9 results in a concentration of 2,900 µg/l. However, since there is a lower value (2,100 µg/l) from a flow-through test with measured concentrations, the Final Fish Acute Value is 2,100 µg/l.

Adjustment of the two test results with Daphnia magna under different testing procedures results in the values becoming more similar, 318 and 354 µg/l (Table 2), and therefore the Guideline's adjustment factors for test conditions appear correct for selenium. The Final Invertebrate Acute Value derived from these data is 16 µg/l and, since this concentration is lower than the equivalent concentration for fish, it also becomes the Final Acute Value.

Chronic Toxicity

No published data are available on the chronic toxicity of selenium to freshwater organisms except for the 46- to 96-day LC50 values in Table 5. These results will be discussed later in this document.

Plant Effects

Selemium is quite toxic to two algal species (Hutchinson and Stokes, 1975) with growth being retarded at 50 µg/l (Table 3). These results indicate that the plants need further investigation with regard to toxic effects of selenium.

Residues

Bioconcentration factors have been determined for the rainbow trout, fathead minnow, and bluegill (Adams, 1976 and U.S. EPA, 1978) and these factors range from 2 to 20. The tissue half-llife for the bluegill (U.S. EPA, 1978) was between 1 and 7 days. These results suggest that tissue accumulation of selenium should not present a hazard to aquatic organisms. Since no maximum permissible tissue concentration is available, no Residue Limited Toxicant Concentration can be calculated.

Miscellaneous

Data in Table 5 indicate that mortality of fish species continues to occur after the usual 96-hour time used for most toxicity tests. The 96-hour LC50 for goldfish is 26,060 µg/l (Cardwell, et al. 1976) and mortality occurred at 2,000 and 5,000 µg/l after 46 and 10 days, respectively (Ellis, 1937). Fathead minnow 96-hour LC50 values (Cardwell, et al. 1976) were 2,060 and 5,200 µg/l and the 48-day LC50 values were 913 and 460 µg/l (Adams, 1976). The 48-day LC50 (73 µg/l) for coho salmon and the 96-day LC50 (128 µg/l) for rainbow trout (Adams, 1976) are much lower than the 96-hour LC50 (10,180 µg/l) for brook trout (Cardwell, et al. 1976).

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations are expressed in terms of selenium.

Final Fish Acute Value = 2,100 µg/l

Final Invertebrate Acute Value = 16 µg/l

Final Acute Value = 16 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 50 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 50 µg/l

0.44 x Final Acute Value = 7.0 µg/l

No freshwater criterion can be derived for selenium using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available.

However, tests (Gary Kimball, personal communication, University of Minnesota, St. Paul, Minn.) which have been completed so recently that written reports on them are not yet available, provide enough additional data to allow the derivation of a criterion. The tests were performed using selenous acid (H_2SeO_3), but the following results are expressed as µg selenium/l:

1. Fathead minnow (juvenile), Pimephales promelas, flow-through, measured concentrations, 96-hour LC50 = 940 µg/l. Adjusted LC50 = 940 µg/l.

2. Cladoceran, Daphnia magna, static, measured concentrations, 48-hour EC50 = 1,200 µg/l. Adjusted LC50 = 1,300 µg/l.

3. Fathead minnow, Pimephales promelas, embryo-larval test, limits = 153-303 µg/l, chronic value = 110 µg/l.

4. Cladoceran, Daphnia magna, life cycle test, limits = 190-300 µg/l, chronic value = 240 µg/l.

Using these values with those in the attached tables gives the following:

Final Fish Acute Value = 940 µg/l

Final Invertebrate Acute Value = 22 µg/l

Final Acute Value = 22 µg/l

Final Fish Chronic Value = 16 µg/l

Final Invertebrate Chronic Value = 47 µg/l

Final Plant Value = 50 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 16 µg/l

0.44 x Final Acute Value = 9.7 µg/l

To derive the criterion for selenium, the maximum concentration is the Final Acute Value of 22 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on freshwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For selenium the criterion to protect freshwater aquatic life as derived using procedures other than the Guidelines is 9.7 µg/l as a 24-hour average and the concentration should not exceed 22 µg/l at any time.

Table 1. Freshwater fish acute values for selenium (Cardwell, et al. 1976)

Organism	Bioassay Method*	Test Conc. **	Time (hrs.)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Brook trout (adult), Salvelinus fontinalis	FT	M	96	10,180	10,180
Goldfish (juvenile), Carassius auratus	FT	M	96	26,060	26,060
Fathead minnow (fry), Pimephales promelas	FT	M	96	2,060	2,060
Fathead minnow (juvenile), Pimephales promelas	FT	M	96	5,200	5,200
Channel catfish (juvenile), Ictalurus punctatus	FT	M	96	12,960	12,960
Flagfish (juvenile), Jordanella floridae	FT	M	96	6,480	6,480
Bluegill (juvenile), Lepomis macrochris	FT	M	96	28,500	28,500

* FT = flow-through

** M = measured

Geometric mean of adjusted values = 11,296 µg/l $\quad \frac{11,296}{3.9} = 2,900$ µg/l

Lowest value from a flow-through test with measured concentrations = 2,100 µg/l

Table 2. Freshwater invertebrate acute values for selenium

Organism	Bioassay Method*	Test Conc.**	Time (hrs.)	LC50 (ug/l)***	Adjusted LC50 (ug/l)***	Reference
Scud, Hyallela azeteca	FT	M	96	318	318	Adams, 1976
Cladoceran, Daphnia magna	S	U	48	430	364	U.S. EPA, 1978

* S = static, FT = flow-through

** U = unmeasured, M = measured

*** Converted from compound to selenium

Geometric mean of adjusted values = 340 µg/l $\frac{340}{21}$ = 16 µg/l

Lowest value from a flow-through test with measured concentrations = 320 µg/l

Table 3. Freshwater plant effects for selenium (Hutchinson & Stokes, 1975)

Organism	Effect	Concentration (ug/l)
Alga, *Chlorella vulgaris*	Growth retardation	50
Alga, *Haematoccus cupensis*	Growth retardation	50

Lowest plant value = 50 ug/l

Table 4. Freshwater residues for selenium

Organism	Bioconcentration Factor	Time (days)	Reference
Rainbow trout, *Salmo gairdneri*	2	48	Adams, 1976
Fathead minnow, *Pimephales promelas*	9	96	Adams, 1976
Bluegill, *Lepomis macrochirus*	20	28	U.S. EPA, 1978

Table 5. Other freshwater data for selenium

Organism	Test Duration	Effect	Result (ug/l)	Reference
Cladoceran, Daphnia magna	24 hrs	LC50	16,000	Bringmann & Kuhn, 1977
Coho salmon, Oncorhynchus kisutch	48 days	LC50	73	Adams, 1976
Rainbow trout, Salmo gairdneri	96 days	LC50	128	Adams, 1976
Goldfish, Carassius auratus	46 days	Gradual anorexia and mortality	2,000	Ellis, et al. 1937
Goldfish, Carassius auratus	10 days	Mortality	5,000	Ellis, et al. 1937
Goldfish, Carassius auratus	7 days	LC50	12,000	Weir & Hine,.1970
Carp (larva), Cyprinus carpio	-	Mortality	1,000 synergistic interaction with 3,000 ug Hg	Huckabee & Griffith, 1974
Fathead minnow, Pimephales promelas	48 days	LC50	913	Adams, 1976
Fathead minnow, Pimephales promelas	48 days	LC50	460	Adams, 1976
Creek chub, Semotilus atromaculatus	48 hrs	Mortality	≥12,000	Kim, et al. 1977
Bluegill, Lepomis macrochirus	48 days	LC50	182	Adams, 1976

SALTWATER ORGANISMS

Introduction

Acute static test results are available for one fish, one invertebrate, and one algal species. In addition, there is a life-cycle test with the mysid shrimp. No adverse effects on these organisms were observed at concentrations as high as 127 µg/l.

Acute Toxicity

The adjusted 96-hour LC50 value for the sheepshead minnow was 3.668 µg/l and, after division by the Guideline's sensitivity factor of 3.7, the resultant Final Fish Acute Value is 990 µg/l (Table 6). The mysid shrimp was slightly more sensitive with an adjusted 96-hour LC50 value of 508 µg/l (Table 7). This datum is used to derive the Final Invertebrate Acute Value of 10 µg/l, which becomes the Final Acute Value since it is lower than the comparabale result for fish.

Chronic Toxicity

The mysid shrimp has been exposed to selenium for its life cycle and the chronic value is 135 µg/l (Table 8). Since this is the only chronic datum, it is divided by the species sensitivity factor of 5.1 to obtain the Final Invertebrate Chronic Value of 26 µg/l. This is the lowest chronic value and it, therefore, becomes the Final Chronic Value.

Plant Effects

The saltwater alga, Skeletonema costatum, has been tested with selenium (U.S. EPA, 1978) and the 96-hour EC50 values for chlorophyll a and cell numbers are 7,930 and 8,240 µg/l, respectively (Table 9). The former becomes the Final Plant Value.

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations are expressed in terms of selenium.

Final Fish Acute Value = 990 µg/l

Final Invertebrate Acute Values = 10 µg/l

Final Acute Value = 10 µg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = 26 µg/l

Final Plant Value = 7,900 µg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 26 µg/l

0.44 x Final Acute Value = 4.4 µg/l

To derive the criterion for selenium, the maximum concentration is the Final Acute Value of 10 µg/l and the 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentrations.

CRITERION: For selenium the criterion to protect saltwater aquatic life as derived using the Guidelines is 4.4 µg/l as a 24-hour average and the concentration should not exceed 10 µg/l at any time.

Table 6. Marine fish acute values for selenium (U.S. EPA, 1978)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Sheepshead minnow, *Cyprinodon variegatus*	S	U	96	6,710	3,668

* S = static

** U = unmeasured

Geometric mean of adjusted values = 3,668 µg/l $\frac{3,668}{3.7}$ = 990 µg/l

Table 7. Marine invertebrate acute values for selenium (U.S. EPA, 1978)

Organism	Bioassay Method *	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)
Mysid shrimp, *Mysidopsis bahia*	S	U	96	600	508

* S = static

** U = unmeasured

Geometric mean of adjusted values = 508 µg/l $\frac{508}{49}$ = 10 µg/l

Table 8. Marine invertebrate chronic value for selenium (U.S. EPA, 1978)

Organism	Test*	Limits (ug/l)	Chronic Value (ug/l)
Mysid shrimp, *Mysidopsis bahia*	LC	127-143	135

LC = life cycle or partial life cycles

Geometric mean of chronic values = 135 µg/l $\frac{135}{5.1}$ = 26 µg/l

Lowest chronic value = 135 µg/l

Table 9. Marine plant effects for selenium (U.S. EPA, 1978)

Organism	Effect	Concentration (ug/l)
Alga, *Skeletonema costatum*	96-hr EC50 chlorophyll a	7,930
Alga, *Skeletonema costatum*	96-hr EC50 cell count	8,240

Lowest plant value = 7,930 µg/l

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SELENIUM

EXPOSURE

Ingestion

Water. The U.S. EPA (1975a) reported that only one sample out of 418 analyzed for Interstate Carrier Water Supplies in 1975 exceeded the drinking water limit of 10 µg/l. According to Craun, et al. (1977), a study of home tap water samples collected from 3,676 residences located in 35 geographically dispersed areas found only 9.96 percent of the samples with selenium levels above the detection limit of 1 µg/l. The average, minimum, and maximum of the mean selenium levels detected in the 35 areas were 3.82 µg/l, 1.0 µg/l, and 36.8 µg/l, respectively.

Smith and Westfall (1937) found measurable amounts (50 to 330 µg/l) of selenium in drinking waters from 10 of 44 wells in a seleniferous area of South Dakota. Hadjimarkas (1965) found averages of 2, 1 and less than 1 µg/l for 21, 23 and 28 farm samples from three Oregon counties.

Sewage plant effluents may contribute to the selenium content of water; as much as 280 µg/l have been reported in raw sewage, 45 µg/l in primary effluent, and 50 µg/l in secondary effluent (Baird, et al. 1972).

Food. Selenium concentrations in plants depend largely on the concentration and availability of selenium in the soil where the plants are grown. For example, in South Dakota, whole milk may contain up to 1,200 µg/l of selenium, whole eggs as much as 10 µg/l of selenium, and vegetables (string beans, lettuce, turnip leaves, and cabbage) from 2 to 100 µg/g (National Research

Council, 1977).

A number of investigators have found samples of wheat and wheat products that contain 1 to 4 µg/g of selenium (Lakin and Byers, 1941; Robinson, 1936).

Additional information on selenium levels in food are shown in Tables 1 to 4. Table 1 lists the selenium content of staple foods of the American diet (Morris and Levander, 1970). The relationship of selenium levels in foods grown in seleniferous and non-seleniferous soils is in Table 2. Several estimates on the average daily intake of selenium by humans are presented in Table 3, while Table 4 reports the estimated daily intake of a 6-month-old infant.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. Since BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the 19 major species identified in the survey, the relative consumption of the four major groups can be calculated.

Tests on the bioconcentration of selenium by aquatic animals have only been conducted with three species of freshwater fish. The tests with rainbow trout and fathead minnows (Adams, 1976) gave BCF values of 2 and 9 respectively for the whole body. The test with the bluegill (U.S. EPA, 1978) lasted 28 days and gave a BCF of 20 for whole body. Based on data for lead and cadmium, selenium would probably have a lower BCF for fish and decapod muscle than for fish whole body, but probably would have a higher BCF for molluscs.

Group	Consumption (Percent)	Bioconcentration factor
Freshwater fishes	12	5
Saltwater fishes	61	5
Saltwater molluscs	9	150
Saltwater decapods	18	5

Using the data for consumption and bioconcentration for each of these groups, the weighted average BCF for selenium is 18 in consumed fish and shellfish.

Inhalation. Zoller and Reamer (1976) reported that most urban regions have concentrations of particulate selenium ranging from 0.1 to 10 ng/m^3. Air samples collected at Cambridge, Mass. Averaged 1 ng/m^3 of selenium (Hashimoto and Winchester, 1967), while Dams, et al. (1970) found selenium values of 2.5 ng/m^3 at Niles, Mich. and 3.8 ng/m^3 at East Chicago, Ind.

Eighteen air samples collected around Buffalo, N.Y. during 1968-1969 had selenium levels ranging between 3.7 and 9.7 ng/m^3, with an average of 6.1 ng/m^3 (Pillay, et al. 1971).

Dermal. Selenium has a large number of industrial uses, and most dermal exposures of signifance would be primarily confined to occupational exposures. Dermatitis has been observed on the hands of workers handling elemental selenium (Amor and Pringle, 1945). Selenium dioxide has also caused dermatitis (Pringle, 1942) and burns when in contact with the eyes (Middleton, 1947). When allowed to penetrate below the fingernails, selenium dioxide has caused painful inflammatory reactions (Glover, 1954).

Some antidandruff shampoos contain 1 to 2.5 percent selenium sulfide or selenium disulfide (Cummins and Kimura, 1971; Orentreich and Berger, 1964;

National Research Council, 1976). Cummins and Kimura (1971) described an unpublished study which showed that ordinary application of a shampoo containing 1 percent selenium sulfide for 1 year did not result in a significant elevation of selenium levels in the blood when compared with controls. The authors concluded that no apparent percutaneous absorption of selenium occurred following one year of age.

PHARMACOKINETICS - Human Data Supplemented by Other Mammalian Species When Pertinent

Absorption. Thomson and Stewart (1973) conducted a study in female Wistar rats to estimate gastrointestinal absorption rates for selenite and selenomethionine. Two groups of twenty rats received a measured dose of approximately 5 µCi [^{75}Se] selenomethionine containing not more than 5 µg Se, one group by intravenous injection and the other by intragastric intubation. Another two groups of twenty rats received intravenous or oral doses of [^{75}Se] selenite, again containing not more than 5 µg Se. Three methods were employed for estimating intestinal absorption yielding a percentage range of 91 to 93 and 95 to 97 for selenite and selenomethionine respectively.

In a subsequent study, Thomson, et al. (1975a) estimated the intestinal absorption of selenocystine and selenomethionine for two groups of twenty five female Wistar rats. The method of exposure was gastric intubation and the dose levels were (approximately 5 µCi) of [^{75}Se] selenocystine and (approximately 2 µCi) of [^{75}Se] selenomethionine. Each dose contained not more than 5 µg Se. Estimated absorption of [^{75}Se] selenocystine was 81.1 percent of the administered dose and that of [^{75}Se] selenomethionine was 86.4 percent of the dose.

Thomson and Stewart (1974) have also investigated gastrointestinal absorption rates in three young women aged 33, 20 and 25 years respectively.

The mean height and weight were 1.6 m and 57 kg respectively. While fasting, each received a measured oral dose of approximately 10 μCi [^{75}Se] selenite containing not more than 10 μg Se. Calculated intestinal absorption rates for the three women were 70, 64, and 44 percent of the administered dose.

The literature contains practically no quantitative data on the pulmonary absorption of gaseous or finely dispersed particulate selenium compounds (National Research Council, 1976). For purposes of extrapolating air standards to drinking water standards, Stokinger and Woodward (1958) assume that both the pulmonary and gastrointestinal absorptive factors are 80 percent of appropriately administered doses.

Little quantitative information is available concerning the dermal absorption of selenium compounds (National Research Council, 1976).

Distribution. Dudley (1936) investigated the distribution of selenium in domestic farm animals fed sodium selenite or selenium bearing plants. A hog, calf, and sheep were fed sufficient selenium (19.64 mg/kg, 20 mg/kg, 11.21 mg/kg for the hog, calf, and sheep respectively) to induce prompt fatal outcome within 6 hours to 3 days. For the hog, sheep, and calf the level of selenium in the blood amounted to 5, 7, and 27 μg/ml respectively. The tissues with the highest selenium levels were the liver, kidney and spleen. The heart, lungs, brain, and muscle of the three species contained lesser amounts of the element.

Handreck and Godwin (1970) introduced a ^{75}Se labelled pellet (1.0 g elemental selenium and 1/4 mCi activity) into the rumen of each of 8 sheep (4 raised on selenium adequate diets and 4 on selenium deficient diets) and monitored them in metablic cages for a period of one month prior to sacrifice. ^{75}Selenium was detected in every tissue examined. The highest levels were

found in kidney cortex and medulla, liver, and various glandular tissues. Lowest levels were found in fat, bile, grey marrow and parts of the eye. Initial selenium status of the animals had little effect on the resulting overall distribution.

Kincaid et al. (1977) investigated the distribution of selenium in three groups of 5 male Holstein calves, approximately 120 days old and 105 kg, fed a practical diet (containing 0.3 µg/g Se) supplemented with 0, 0.1, or 1.0 µg/g added selenium, as sodium selenite. After 28 days on the experimental diets, the calves were orally dosed with 608 µCi ^{75}Se (specific activity 93 mCi/mg Selenium) via gelatin tablets. The calves were sacrificed forty eight hours after dosing. The general effect of the supplemental dietary selenium on tissue ^{75}Se uptake of an oral ^{75}Se dose is reflected by the blood data. Blood ^{75}Se concentrations were reduced about 15% and 35% with 0.1 µg/g and 1.0 µg/g added dietary selenium, respectively. The kidney, the middle and lower small intestine, and the liver retained the greatest amounts of ^{75}Se for all groups.

Using information collected for 94 pigs included in a Canadian Government supported study of the effects of dietary copper supplementation, Young, et al. (1977) have investigated the statistical relationships between dietary selenium (0.06 to 0.61 µg/g dry matter) and liver selenium (0.93 to 2.76 µg/g dry matter) and longissimus muscle selenium (0.38 to 1.84 µg/g dry matter). The resultant estimation equations are as follows: Liver Se = 0.971 + 5.79 Diet Se - 4.74 Diet Se^2, R^2 = 5.15; Muscle Se = 0.154 + 5.264 Diet Se - 4.526 Diet Se, R^2 = 63.3.

In summary, the primary deposition sites for selenium in the body are the liver, kidney, spleen, and middle and lower sections of the small intestine followed by the heart, lungs, brain, and muscle. Based on the work of Kincaid, et al. (1977) it is apparent that actual tissue concentration levels are affected both by dose level and levels in the normal diet, but the primary deposition sites remain the same.

Metabolism. The National Research Council (1977) at the request of, and funded by, the U.S. Environmental Protection Agency under contract no. 68-01-3139 has thoroughly summarized and reviewed the literature concerning the biotransformation aspects of selenium metabolism. Hence the material in this section is quoted from that review.

> Little is known about the biochemistry of selenium in mammalian systems. At concentrations required nutritionally, selenium is incorporated into specific functional proteins; at higher concentrations, it is incorporated into molecules normally served by sulfur. Selenium analogs are often less stable than sulfur compounds, and this lability may be the basis of toxicity. Selenium biochemistry has been the subject of recent reviews (Stadtman, 1974).
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> By the mechanism used for sulfate ion, microorganisms are capable of activating selenate with adenosine triphosphate (Wilson and Bandurski, 1956), but it is not clear that appreciable amounts of activated selenate are reduced to selenite via 3'-phosphoadenosine-5'-phosphoselenate, which would be directly analogous to the recognized reduction of activated sulfate to sulfite by phosphoadenosine phosphosulfate. In animals, phosphoadenosine phosphosulfate is important in the formation of sulfate esters in the detoxication of foreign compounds and the metabolism of steroids and other indigenous compounds (Lipmann, 1958); the activity of 3'-phosphoadenosine-5'phosphoselenate, if formed, in formation of selenate esters is not known. Although selenate and selenite ions are absorbed and incorporated into organic molecules as selenide, it is not fully known how the reduction of selenium is accomplished (Stadtman, 1974).
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> Selenite is methylated by mammalian tissues in an apparent detoxication process. Mouse liver and kidneys use S-adenosylmethionine and reduced glutathione to form dimethylselenide from selenite (Ganther, 1966); the lungs are also active in the methylation, but muscle, spleen, and heart have little activity. Dimethylselenide is less toxic than sodium selenite (McConnell and Portman, 1952).
>
> Selenite and selenate are metabolized to trimethylselenonium ion, $(CH_3)_3Se^+$, which is the principal excretory product of selenium in urine (30 to 50 percent of the urinary selenium) (Byard, 1968; Palmer et al. 1969, 1974). Again, trimethylselenonium ions are less toxic than selenite or selenate ions (Obermeyer et al. 1971). Although these methylated products are less toxic than the parent selenium compounds, they are involved by unknown mechanisms in synergistic toxicity; dimethylselenide and mercury toxicities are synergistic (Parizek et al. 1971), as are those of trimethylselenonium ion and arsenic (Obermeyer et al. 1971).
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> In mammalian systems, inorganic selenium usually is not incorporated into amino acids (Cummins and Martin, 1967), although there is some evidence of the incorporation of selenium from sodium selenite into a rabbit protein (Godwin and Fuss, 1972). The matter is confusing, because inorganic selenium can be reduced to complex with disulfides to give

selenodisulfides (R-S-Se-S-R), as is the case with two molecules of cysteine (Painter, 1941; Ganther, 1968) or reduced glutathione (Ganther, 1971).

Selenium appears to serve as an essential element in some oxidation-reduction processes in mammals. Sheep skeletal muscles contain a small (mol. wt., 10,000) selenoprotein that has a heme group. Although the selenium appears to be an integral part of the protein, its position and function in the protein are not known (Pedersen et al. 1973).

A second selenoprotein is known: glutathione peroxidase, an enzyme, catalyzes the reduction of hydrogen peroxide. The activity of glutathione peroxidase in red cells of seleniumdeficient animals is low, but may be restored specifically by selenium administration (Roturck et al. 1973). The enzyme has a molecular weight of 84,000 and is composed of four subunits of molecular weight 21,000 each; each subunit contains one atom of selenium (Flohe et al. 1973).

Excretion. Rosenfeld (1964) has investigated the effects of mode and frequency of selenium administration on urinary, fecal, and respiratory excretion rates in male and female Sprague-Dawley rats (weight of females 200-300 g; weight of males 300-450 g). After a single tracer dose of 7.5 µg of ^{75}Se the percent of administered dose excreted in 24 hours in the urine and feces for each mode of administration are: subcutaneous 12.9 and 3.7 percent; intraperitoneal 26.0 and 4.0 percent; intragastric 34.0 and 13.9 percent. For tracer doses it does not appear that repeated administration (by various routes) alters the total elimination pattern observed after a single dose, but the amount excreted by the kidney, gut, and lung show some differences. The primary mode of elimination for tracer doses is the urinary tract. Forty percent of the injected dose is excreted in the urine and about one-half or less is excreted by the gastrointestinal tract and lung. Selenium was eliminated by the urinary, gastrointestinal, and respiratory tracts up to 150 days. Respiratory elimination ceased three days after subcutaneous injections. Administration of repeated subacute doses (2.5 mg of selenium (H_2SeO_3)/kg mixed with ^{75}Se ($H_2{}^{75}SeO_3$)) resulted in a reversal of the route of elimination as indicated by the decreased rate of urinary excretion and

increased excretion of ^{75}Se in the feces and by the lung.

Thomson and Stewart (1973) and Thomson, et al. (1975a) have determined urinary and fecal excretion rates for Wistar rats exposed to [^{75}Se] selenocystine, [^{75}Se] selenomethionine, and [^{75}Se] selenite by oral administration. Two groups of twelve female rats bred from the same colony and initially weighing 90-120 g were maintained on tap-water and a pelleted stock diet containing 180 g available protein and 0.025 mg Se/kg. The rats in one of the groups were anaesthetized with 5 mg sodium pentobarbitone and given by gastric intubation a known amount (approximately 5 µCi) of [^{75}Se] selenocystine. The same procedure was used to administer a known amount (approximately 2 µCi) of [^{75}Se]-selenomethionine to the second group. Two groups of twelve female rats, initially weighing 140 to 160 g, were exposed by the same procedures to 5 µCi [^{75}Se] selenomethionine and [^{75}Se] selenite respectively. None of the dose levels for the 4 groups contained more than 5 µg Se. After exposure the rats were placed in metabolic cages for the separate collection of urine and feces. These collections were completed at 24 hour intervals for 7 days. The percentages of administered doses excreted (during the first week after the oral dose) in the urine and feces for each set of animals are as follows:

	Urine	Total Fecal
[^{75}Se] selenocystine (5 µCi)	11.4	27.1
[^{75}Se] selenomethionine (2 µCi)	5.0	22.2
[^{75}Se] selenomethionine (5 µCi)	4.2	15.6
[^{75}Se] sodium selenite	12.7	20.6

The relationships between selenium dose and that excreted in the respiratory gases have been researched by McConnel and Roth (1966). Young adult male rats were injected subcutaneously with a single dose of selenium either as selenite ($^{75}SeO3$) or L-seleno-75 methionine to which was added amounts of the correspondent stable selenium compound. The doses of selenite ranged from

0.005 to 5.410 mg/kg with corresponding ranges of 24 hour excretion for exhaled air and urine of 0.2 to 52 percent and 32.9 to 1.9 percent respectively. Dose levels for L seleno 75 methionine ranged from 0.001 to 5.583 mg/kg with corresponding exhaled air and urine excretion percentages of 1.3 to 35.9 and 27.10 to 6.82 respectively.

Selenium excretion as a percent of administered dose had also been studied in humans (Waterlow, et al. 1969; Thomson and Stewart, 1974). Waterlow, et al. (1969) gave each of eight infants a single dose of 0.1 μCi [^{75}Se] methionine/kg body weight (six infants received oral dose and two intravenous); the human subjects were male infants, aged 7-16 months, admitted to the hospital with severe malnutrition. All but one of the infants were on a high protein diet (3-5 g/kg/day) at the time when the study began. Forty-eight hour excretion levels were reported for only 3 of the 6 infants that received oral doses and for both intravenous exposed infants; the twenty four hours instead of the 48 hours excretion level was reported for 1 of the infants and nothing was presented for the other two infants. Ranges of 48-hour urinary and fecal excretion percentages are: oral (3.2 to 7.25 for urine and 3.6 to 15.15 for feces); intravenous (8.6 to 8.95 for urine and 1.7 to 2.95 for feces). The 24-hour excretion percentages of the one orally exposed infant are 4.5 for urine and 8.1 for feces. When selenomethionine was given by mouth, during the first 48 hours more radioactivity was lost in the feces than the urine. When the isotope was given by vein the greater part of the loss occurred in the urine. In the subjects that received selenomethionine orally the loss in the feces tended to remain higher than that in the urine for about the first 10 days. However, the fecal loss, expressed as percent of retained dose per day, declined as time went on, whereas the rate of loss in the urine remained rather constant.

Thomson and Stewart (1974) studied selenium excretion by feeding three women aged 33, 20, and 25 years (mean height of 1.60 meters and weight of 57 kg) an oral dose of approximately 10 μCi [^{75}Se] selenite containing not more than 10 μg Se; the women were fasting at the time of administration. In the first 24 hours after the dose of ^{75}Se, urine was collected every hour for 10 hours, then every 2 hours for 6 hours and finally at the end of 8 hours. Subsequently, 24 collections were made daily for the next 13 days. A gelatin capsule containing 50 mg brilliant blue marker and 200 mg methyl cellulose was swallowed immediately after the ^{75}Se dose. All individual stools for at least 14 days were collected separately. Thereafter a single fecal sample was obtained each week on the day of the urine collection. Expired air from each subject was collected in Douglas bags for 8-10 minute periods at regular time intervals during the first 9 hours. Dermal loss was measured by analysis of underclotting. Urine and fecal excretion, expressed as a percent of dose, for the first 2 weeks were 7 to 14, and 58 to 33 respectively. No radioactivity was detected in the Douglas bags containing expired air. However, on day 1, traces of ^{75}Se of less than 0.02 percent of the dose were found in the HNO_3 and mecuric chloride solutions through which expired air had been passed, but there was no ^{75}Se in the air collected on day 2. No radioactivity was detected in the underclothing worn during the first, second, or third day.

Based on these studies, it is apparent that the primary routes of excretion are in the urine and feces and that the distribution between the two depends on the level of exposure and length of time subsequent to exposure.

EFFECTS

Nutritional Deficiency. Since the late 1950's, a number of researchers have demonstrated the essentiality of selenium for several animal species (Ganther, 1970; Schwarz, 1961). Selenium deficiency has resulted in white muscle disease in ruminants, hepatic degeneration and peridontal disease in

other mammals, such as rats, swine, and sheep, and diathesis, poor growth, and fibrotic degeneration of the pancreas in poultry (Desai, 1967). Although there is no definite proof that selenium is an essential element in human nutrition, observations of children suffering from kwashiokor, the protein malnutrition disease, suggests such a role for selenium (Jaffe, 1973). The possibility of selenium deficiency causing the sudden infant death syndrome (crib or cot death) has not been disregarded (Frost, 1972; Rhead, et al. 1972).

Acute, subacute, and chronic toxicity. The toxic effects of selenium have been recognized much longer than the nutritional ones. The discovery in the 1930's that certain geographical areas are seleniferous and produce plants with high selenium content explained observations dating back centuries that food grown in these areas caused sickness in man and beast consuming it. In addition to the generalized increase of selenium in vegetation from such areas, a few species of plants were identified that thrived there and were termed selenium indicator plants (Rosenfeld and Beath, 1964). These plants characteristically accumulate extremely high levels of selenium in the form of nonprotein selenoamino acids such as Se-methylselenocysteine and produce acute toxicity in animals consuming them (Burk, 1976).

The diseases of "blind staggers," "alkali disease" in cattle and "white muscle" in lambs and calves (a myopathy which results from the feeding of seleniferous legumes to the dams during gestation (Muth, et al. 1958)) have been described by many observers, but the mechanism of toxic action is not completely agreed upon (Browning, 1969).

Blind staggers is the name applied to the acute form of selenium disease, though the animal is not blind and may not stagger. There is some impairment of vision, a difficulty in judging near objects and a general tendency to

wander. Paralysis and evidence of abdominal pain occur in the final stages of the disease; death is due to respiratory failure (Browning, 1969).

Alkali disease is a more chronic form of selenium poisoning of livestock than blind staggers. Primary symptoms are emaciation, lack of vitality, loss of hair from the mane and tail of horses and from the switch of cattle, and in severe cases separation of the hoof. Lambs are born with abnormal eyes, deformed feet and myopathies. Lesions of internal organs are more marked in the heart (atrophy and decompensation) and liver (cirrhosis). The kidneys may show glomerulonephritis and the joints of the long bones erosion. There is also a high incidence of amemia (Browning, 1969).

Acute selenium poisoning in laboratory animals has been produced by a toxic dose of selenium compound administered orally, subcutaneously, intraperitoneally, or intravenously. Sodium selenite and selenate are the most commonly tested selenium salts. The lethal dose has varied in the hands of different observers, owing probably to species differences, age of the animals, mode of administration, and the purity of the salts (Fishbein, 1977). Table 5 summarizes some of the data reported in the literature on the acute toxicity of various selenium compounds.

Although the possibility exists that range animals and man may be exposed to sufficient selenium to result in acute effects, the problem of acute toxicity seems less important than that of chronic toxicity (National Research Council, 1976).

The concentrations of selenium in the diet, or given orally, leading to selenium poisoning (selenosis), depend on the chemical form of selenium and other dietary components (Fishbein, 1977). In general, however, the concentration necessary to produce chronic selenium poisoning has been observed in rats and dogs at dietary levels of 5 to 10 µg/g (Anspaug and Robison, 1971). Chronic effects from prolonged feeding with diets containing added selenium in

amounts of 5 to 15 µg/g include liver damage in the form of atrophy, necrosis, cirrhosis, and hemorrhage, marked and progressive anemia with hemoglobin values as low as 2 g percent in some species (Fishbein, 1977). Vesce (1947) noted changes in endocrine glands, especially the ovaries, pituitary, and adrenals following oral administration of 5 to 12.5 mg sodium selenide to guinea pigs over two periods of 20 days.

The National Research Council (1976) at the request of and funded by the U.S. Environmental Protection Agency under contract no. 68-02-1226 has thoroughly summarized and reviewed the literature concerning selenium toxicity in an attempt to establish a "no effect" dose level for the element. Their summary is quoted here.

> In 1967, Tinsley et al. (1967) concluded that, so far as longevity is concerned, a daily dose of 0.5 mg of selenium as selenite or selenate per kilogram of body weight per day seemed to be the threshold dose in rats on a casein-Cerelose diet (for a 200-g rat eating 10 g of feed per day, this would be the equivalent of 10 µ g/g). On the other hand, a calculated maximum body weight was reported to be decreased by as little as 0.5 µg/g of selenium. In addition, Harr et al. (1967) reported that when additions of 0.5-2 µg/g of selenium were made to the diets, proliferation of the hepatic parenchyma was more prevalent than in control animals on diets with no added selenium and that selenium added to a commercial diet produced less toxicity than selenium added to a casein-Cerelose diet.
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> A complementary report gives detailed data (Bioassay of Selenium Compounds for Carcinogenesis in Rats, 1966). Here again, the weight effects were noted. However, a careful study of the data on chronic liver and bile duct hyperplasia shows that this lesion was even more prevalent in a commercial diet without added selenium than in a casein-Cerelose diet with 0.5 µg/g of added selenium. This may mean that the hyperplasia does not indicate a toxic effect of the element. In a later report, Harr and Muth (1972) state, with reference to the studies of the semipurified diet, that the minimum toxic level for liver lesions was 0.25 µg/g. With reference to longevity and lesions in heart, kidneys, and spleen, they concluded that the minimum toxic level was 0.75 µg/g. They state, however, that rats fed 0.5 µg/g of selenium in the diet grew as well as the controls. They concluded that the estimated dietary threshold for physiologic-pathologic effect is 0.4 µg/g and for pathologic-clinical effects, 3 µg/g. Neither growth nor longevity was adversely affected by as much as 2.5 µg/g of added selenium in a torula yeast diet to which the carcinogen fluorenylacetamide had been added. The physiologic significance of some of the observations of this group is difficult to evaluate."

Pletnikova (1970) has recommended a maximum concentration of 0.001 mg of selenium as selenite or selenate per liter of water for Russian drinking water. She reports 0.01 mg/liter as the threshold for detection by odor. She also reports decreased liver function and effects on the activities of some enzymes along with increased blood glutathione in rats receiving 0.5 µg of selenium per kilogram of body weight per day (about 0.01 mg/liter) for a period of 6 months. These effects were not obtained at a level of one-tenth of this amount. Unfortunately, she does not describe the diet or state its selenium content. Quite likely, the selenium intake from it was considerably greater than that from the water containing 0.01 mg/liter. Further, bromsulphthalein (BSP) clearance was used for the liver-function test. With this, BSP is excreted into the bile conjugated with reduced glutathione (GSH). If selenium catalyzes GSH oxidation, the GSH pool available to react with the dye would be depleted; hence, the effect may not indicate a toxicity. The physiologic significance of the observations made in this study is not clear.

Palmer and Olson (1974) studied the toxicity of selenite and selenate to rats on corn or rye-based diets. They administered selenite or selenate in water at the rate of 2 or 3 mg/liter for a period of 6 weeks. Each form produced a small reduction in rate of gain without mortality. Earlier, Schroeder and Mitchener (1971) reported severe toxicity at the 2 mg/liter level for selenite selenium but not for selenate selenium.

Halverson et al. (1966) fed postweanling rats for 6 weeks on wheat diets containing 1.6, 3.2, 4.8, 6.4, 8.0, 9.6, or 11.2 µg/g of naturally occurring or selenite selenium. Growth was not affected below the 4.8 µg/l level of selenite or the 6.4 µg/g level of selenium from grain. At 6.4 µg/g of selenium or above, restriction of feed intake, increased mortality, increased spleen weight and size, increased pancreas size, reduced liver weight, body weight ratios, and reduced blood hemoglobin were noted. These effects were not observed in rats on diets containing lesser amounts of selenium.

Thapar et al. (1969) found that 8 µg/g of selenium added as selenite to either a practical corn-say diet or a Cerelose-soybean protein diet reduced egg production, weight and hatchability of eggs, body weight, survival rate, and growth of progeny of laying hens fed the diet from 1 day of age for as long as 105 weeks. But no detrimental effects were observed when selenium was added at the rate of 2 µg/g, and it is possible that this addition improved the levability of hens on the Cerelose-soybean protein diet. Similar findings were later reported by Arnold et al. (1973). Much earlier, Poley et al. (1941) reported that 2 µg/g of selenium from grain improves the growth of chicks on a practical-type diet.

Witting and Horwitt (1964) reported that growth curves had shown that the selenium requirement of the tocopherol-deficient rat has a very narrow optimal range. The best growth rate was obtained on the addition of 0.1 µg/g of selenium as selenite. At 0.3 µg/g of selenium, the growth was better than at 0.03 µg/g, but not as good as at 0.1 µg/g. With the diet severely deficient in vitamin E, selenium toxicity was noted at what these authors considered an unusually low level of the element: 0.25 µg/g in the basal diet plus 1 µg/g as selenite.

Obviously the chronic toxicity of selenium will depend on the criteria used to determine the "no-effect" dose level. For the normal diet, 4 to 5 µg/g will usually inhibit growth, and this may be the best indicator of toxicity. In a diet deficient in vitamin E, 1 µg/g may be toxic. During the development of teeth, 1 to 2 µg/g may be toxic if subsequent cariogenesis is used to measure toxicity. Histopathologic observations may suggest that less than 1 µg/g can be toxic. However, the physiologic significance of the observations may not be clear, and the same may be said for biochemical parameters indicating that even lower levels can be toxic. In many areas, livestock are regularly fed diets containing over 0.5 µg/g of the element, and there has been nothing to suggest that they fare less well than animals on diets of lower selenium content.

Information concerning the effects of selenium poisoning in humans has been obtained from epidemiologic studies of persons who live in seleniferous areas and consume locally produced food and drink and from studies of occupationally related selenium exposures.

Shapiro (1973) has prepared an excellent review of selenium toxicity studies in humans. Only some of the salient features of this report will be mentioned here.

Water supplies, even in seleniferous areas of the western United States have not generally been considered a potential source of selenium toxicity in man. However, elevated levels have been found in a few isolated areas. One instance of toxicity, due to selenium contained in an underground water source, was described by Beath (1962). Well water from the Wasatch geological formation in Utah contained 9 mg/l selenium. Chronic selenosis occurred in the children, parents, and a dog drinking the water. No selenium was found in the food. Lassitude, total or partial loss of hair, discoloration and loss of fingernails were symptoms of the condition. A halt in the use of the water brought regrowth of the hair and nails and increased mental alertness.

A systematic epidemiological study by Smith, et al. (1936) of chronic toxicity of selenium in man was carried out in South Dakota, Wyoming, and Nebraska on farms where animals were known to be suffering from "alkali disease." A number of clinical signs in farm workers were attributed to

selenium toxicosis, notably bad teeth, jaundice, chloasma, vertigo, chronic gastrointestinal disease, dermatitis, nail changes, arthritis, edema, lassitude, and fatigue. Analyses were made of the selenium content of the food of these people, and daily selenium intakes of 0.1 to 0.2 mg of selenium per kilogram of body weight were recorded. Nearly all the urine samples tested contained measurable amounts of selenium, and 45 percent of these contained from 0.2 to 1.33 µg/ml.

There was some correlation between the symptoms of selenosis and a urinary content greater than 0.2 µg/ml. In reviewing these findings, Shapiro (1973) states: "These studies suggest, but do not firmly establish, that chronic selenium toxicity of dietary origin exists in man. Only when blood and tissue levels are measured in affected individuals, however, will such conclusions be valid."

For many years, hunters in South America have realized that ingestion of fruit of the monkey pod tree Lecythis ollaria could lead to nausea, vomiting, and generalized hair loss (Kerdel-Vegas, et al. 1965). The toxic compound has recently been isolated and identified as selenocystathionine (Aronow and Kerdel-Vegas, 1965).

Carter (1966) reported the death of a child resulting from the ingestion of gun-bluing compound containing 1.8 percent selenious acid. In this case, which is the only autopsy report describing the histopathology of acute selenium poisoning, there was fulminating peripheral vascular collapse, pulmonary edema, and coma. At autopsy the gastric mucosa was a brick-red color, and marked intestinal vascular congestion was observed. Garlic odor of the breath was present before death but was not detected in any organ postmortem. The lungs were diffusely hemorrhagic, congested, and edematous, but no specific renal or hepatic necrosis was described. Although selenium was identified in

several tissues, the levels were not reported.

Buchan (1947) cites a patient who was said to have developed nervousness, mental depression, metallic taste, vomiting, and pharynitis following the use of selenium red lipstick. Although selenium sulfide used in shampoo is relatively inert, a 46-year-old female using excessive amounts on abraded skin developed progressive generalized tremor, abdominal pain, metallic taste, and a garlic breath odor (Ransone, et al. 1961). These symptoms cleared when the us of the shampoo was discontinued.

Hadjimarkos proposed that an increase in dental caries is one of the toxic signs of excessive selenium intake, and showed that urinary selenium was twice as high in children with a high incidence of caries as in children with a low incidence (Hadjimarkos and Bonhorst, 1961; Hadjimarkos, 1969). However, other studies have shown inconsistent (Muhleman and Konig, 1964) or marginally significant (Ludwig and Biddy, 1969) relationships between prevalence of dental caries and levels of selenium in the diet. It should be noted that an increased incidence of caries was produced in rats fed high levels of dietary selenium (Buttner, 1963).

Selenium may be inhaled as fumes or dust, or absorbed through the skin or gastrointestinal tract. Marked irritation of the nasal conjunctival, and tracheobronchial mucosa occurs rapidly, leading to cough, wheezing, dyspnea, chemical pneumonitis, and pulmonary edema. Low-grade fever may complicate the chemical pneumonitis. Abdominal pain, nausea, vomiting, and diarrhea ensue. Acute and chronic dermatitis of exposed or unexposed areas of the skin commonly occurs (Glover, 1970).

Hepatic necrosis has not been observed following exposure of man to selenium, but detailed analyses of liver function have not been performed. Myocarditis, known to occur in animals poisoned with inorganic selenates, (Harr et al. 1967), has not been reported in humans. Workers ex-

posed to selenium have been noted to complain of nervousness, fatigue, depression, and pallor. A garlic odor of breath (and sweat) due to the pulmonary excretion of dimethyl selenide is one of the first signs of selenium absorption; a similar odor has been observed, however, after absorption of tellurium, because of dimethyl telluride excreted via the lungs. Metallic taste is commonly reported after selenium ingestion (Shapiro, 1973).

Nagai (1959) observed hypochromic anemia and leukopenia in Japanese women and children exposed to selenium in a rectifier manufacturing plant.

Studies have not shown changes in various blood constituents in man to be caused by acute or chronic selenium poisoning; however, selenate or selenite feeding has been found to increase serum cholesterol and aoetic lipids in the rat, (Schroeder, 1968), while hypoglycemia has been produced in rabbits by the injection of selenite (Levine and Flaherty, 1926). Tsuzuki et al. (1960) noted both decreased cholesterol levels and increased urinary protein in mice fed selenium.

Synergism or Antagonism. Interrelationships of selenium toxicity with arsenic, mercury, cadmium, silver, and thallium have been described (Diplock, 1976).

Moxon (1938) established that the chronic and acute toxicity produced by feeding of seleniferous grains containing selenium at 15 µg/g could be alleviated or prevented by administration of arsenic at 5 mg/l as sodium arsenate in the drinking water. It was shown that either arsenate or arsenite was equally effective, and the selenium could be presented as seleniferous grain, selenite, or selenocystine (Moxon, et al. 1944; DuBois, et al. 1940; Moxon, et al. 1945, 1947; Carlson, et al. 1954; Thapar, et al. 1969; Ganther and Baumann, 1962). Ganther and Baumann (1962) used subacute dosages of arsenic and selenium and found that excretion of selenium into the gastrointestinal tract was stimulated by arsenic. Levander and Baumann (1966) demon-

strated that selenium is excreted in the bile of arsenic treated animals. The amount of selenium excreted into the bile of rats prepared with acute biliary fistulas increased by tenfold during the first 3 hours following arsenic administration. When the arsenic to selenium dosage ratio was maintained at 2, arsenic was shown to have an effect on biliary excretion of selenium when the dietary level of selenium was as low as 0.02 mgSe/kg. Levander (1972) suggested that arsenic protection against selenium toxicity may be mediated by combination of arsenic with selenium in the liver through reaction to selenol compounds to form a detoxication conjugate readily passed into the bile.

Parizek, et al. (1974) have recently reviewed the literature concerning the toxicological interactions of cadmium and mercury with selenium. Parizek and Zahor (1956) found that parenteral administration of small amounts of cadmium salts caused hemorrhages and necrosis of the testes in addition to analogous damages in other reproductive organs. Parenteral injection of cadmium salts to premature female rats (Kar, et al. 1959) or to adult rats in persistent oestrus (Parizek, et al. 1968a) results in massive hemorrhages and necrosis in the ovaries. Small amounts of cadmium given during pregnancy produces serious placental damage connected with fetal death (Parizek, 1964). Toward the end of pregnancy the effect of cadmium is accompanied by a highly lethal, "toxemia like" syndrome affecting the mothers (Parizek, 1965).

Kar, et al. (1960) found that the cadmium-induced lesions in the testes could be prevented by the administration of selenium. Mason and Young (1967) reported that the testicular injury produced by single subcutaneous injections of 0.45 mg of cadmium chloride in rats was protected against by half-equimolar selenium dioxide injected at the same time as cadmium. Protection was also provided by daily subcutaneous injections of half-equimolar selenium dioxide given over 6 successive days before cadmium. Parizek et al. (1968b) and Gunn

et al. (1968) found that mortality of rats given lethal doses of cadmium was much reduced by the administration of selenium. Holmberg and Ferm (1969) found that the teratogenicity of cadmium was considerably reduced by selenium. Kar, et al. (1959) and Parizek et al. (1968) found that selenium would prevent the cadmium induced damage to the nonovulating ovary in the rat. Parizek, et al. (1968b) and Parizek (1964) found that administration of selenium could prevent cadmium caused necrosis and destruction of the placenta. Similarly cadmium induced toxemia of pregnancy could be prevented by selenium (Parizek, 1965).

Levander and Argrett (1969) described the effect of mercury salts on the metabolism of selenium. Parizek and Ostadalova (1967) demonstrated that small amounts (0.02 mmole/kg) of sodium selenite (Na_2 SeO_3), when given to rats intoxicated by a lethal dose (0.02 mmole/kg) of mercury ($HgCl_2$), completely protected the kidneys or intestine of these animals and ensured their survival. Further experiments revealed that the protective effect of selenite was not connected with an increased excretion of mercury, but on the contrary, with a marked decrease in mercury elimination through the urine (Parizek, et al. 1971). Levander and Argrett (1969) reported that mercury increased the retention of selenium in the blood, kidneys, and spleen. Parizek, et al. (1971) found that the transport of mercury across the placenta in pregnant rats was decreased by selenium, and less mercury was secreted into the milk. The bioavailability of selenium was much lower in the rats treated with mercury. Ganther, et al. (1972) showed that Japanese quail given 20 ug/g of mercury as methylmercury in diets containing 17 percent tuna survived considerably longer than quail given the same amount of methylmercury in a corn-soya diet. It was also found that when a number of different batches of tuna were analyzed for mercury and selenium, there was a striking correlation between the levels of selenium and mercury; those batches that had little

selenium contained little mercury (1.91 µg/g Se: 0.32 µg/g Hg), and when the mercury level was high the selenium level was also high (2.91 µg/g Se: 2.97 µg/g). It suggested that the selenium in the tuna reduced the toxicity to the quail of the added 20 µg/g of methylmercury, which was lethally toxic to birds given the corn-soya diet. In an experiment with rats fed a basal diet containing 20 percent casein with and without the addition of selenium at 0.5 µg/g as sodium selenite, it was found that mercury at 10 µg/g as methylmercury produced 100 percent mortality after 6 weeks of feeding, but selenium was completely effective in preventing mortality.

Diplock et al. (1967) and Grasso et al. (1969) found the 0.15 percent of silver acetate in the drinking water produced toxicity symptoms in rats and chickens fed vitamin E deficient diets; rats suffered from dystrophic lesions, necrotic degeneration of the liver, and high mortality and chickens suffered a proexudative effect. Supplementation with selenium (0.05 µg/g) had little effect, whereas the addition of 1 µg/g of selenium to the diet resulted in 55 percent protection against the toxic effects of silver. Grasso, et al. (1969) studied the lesions produced in the liver by silver and the lesions caused by dietary deprivation of vitamin E and selenium. The lesions were similar.

Hollo and Zlatarov (1960) demonstrated that death due to thallium poisoning could be prevented by the parenteral administration of selenate. Rusiecki and Brzezinski (1966) found that oral administration of selenate prevented the toxicity of thallium and that the content of thallium in liver, kidneys, and bones was increased by the selenate. Levander and Argrett (1969) showed that subcutaneous injection of thallium acetate increaed the retention of selenium in liver and kidney and decreased the pulmonary and urinary excretion of selenium.

Halverson and Monty (1960) have demonstrated that dietary sulfate will

partially restore selenium poisoned rats receiving a purified diet with selenium added as selenite or selenate. Sulfate levels of 0.29, 0.58, and 0.87 percent as sodium or as potassium salts progressively relieved the growth inhibition due to selenium. Alleviations of greater than 40% were observed. Sulfate, however, did not substantially prevent liver degeneration due to selenium. In a later study, Halverson, et al. (1962) found that the addition of sodium sulfate to diets containing 10 µg/g of selenium was added as selenate, but did not when it was added as selenite or as wheat containing selenium. A similar but less pronounced effect was observed with sodium thiosulfate and sodium sulfite added to the seleniferous diets.

Levander and Morris (1970) used a peanut-meal diet and found that neither methionine nor vitamin E alone gave much protection against hepatic damage produced by excessive selenium. Combinations of methionine and vitamin E were effective, and the degree of protection was approximately proportional to the concentration of vitamin E added to the diet. Selenium concentrations of the liver and kidneys from rats fed the diets supplemented with methionine and vitamin E were less than those of the same organs from rats fed either methionine or vitamin E alone or no supplement.

Moxon and Dubois (1939) demonstrated that fluoride increases the toxicity of selenium in rats. They added 5 mg/l of fluoride to the drinking water of rats fed a diet containing selenium at 11 µg/g as seleniferous grain. Mortality was increased while weight gains and feed and water intake decreased. Hadjimarkos (1969) tested the interaction of selenium and fluoride by feeding both elements at levels 3 and 50 mg/l to one group of rats and only selenium at 3 mg/l to another group of rats. He did not observe an increase in the severity of signs of selenium toxicity in the group that received both fluoride and selenium.

Mutagenicity. Fishbein (1977) has recently reviewed the literature concerning the cytogenic and mutagenic effects of selenium. Selenium has been shown to affect the genetic process in barley (Walker and Ting, 1967) and in Drosophila melanogaster (Ting and Walker, 1969; Walker and Bradley, 1969). Treatment with sodium selenite before meiosis caused structural alterations in the meiotic chromatin and decreased the genetic recombination in barley (Walker and Ting, 1967). Genetic crossing-over in D. melanogaster was reduced by selenoamino acids. For example, selenocystine at 2 μM had a significant effect on crossing-over in the X-chromosome of D. melanogaster (Ting and Walker, 1969; Walker and Bradley, 1969). They found that urethane and selenocystine interacted antagonistically at certain levels and synergistically at other levels.

Sentein (1967) found that selenates and selenites have an effect on segmentation mitoses similar to that of SeO_2: polar dissociation with conserved dominance of the principal pole, stickiness, and clumping of chromosomes. Fukina and Kudryavtseva (1969) found that sodium selenite solution caused cell degenerative changes and decreased the mitotic activity when added to kidney tissue cultures of rabbits and pigs in 10^{-1} to 10^{-4} dilutions. Tissue culture was not affected by the application of sodium selenite in 10^{-5} dilutions.

Patton and Allison (1972) have reported concerning the effects of sodium selenate and sodium selenite on chromosomes in cultures of human leukocytes and diploid fibroblasts. Subtoxic doses of sodium selenate and sodium selenite were added to leukocyte cultures and fibroblast cells at various times between 2 and 24 hours before fixation. No chromosome aberrations were observed for either selenium salt; cells were exposed to at least 2 concentrations of each selenium salts for 24, 48, or 72 hours.

Craddock (1972) reported that selenomethionine acts as a methyl donor in

the methylation of DNA, transfer RNA, and ribosomal RNA in the intact rat. The relative amounts of the different methylated bases formed in each nucleic acid were similar to those found after injection of [^{14}C] methylmethionine. He has suggested that it is likely that selenoadenosylselenomethionine (Se-A SeM), which is known to be formed from selenomethionine in vivo, is a methyl donor in no way different from S-adenosylmethionine in the reactions catalyzed by the nucleic acid methylating enzymes.

Teratogenicity. The National Research Council (1976) at the request of and funded by the U.S. Environmental Protection Agency under contract No. 68-02-1226 has thoroughly summarized and reviewed the literature concerning the teratogenic effects of exposure to selenium compounds. Hence the material in this section is quoted from that review.

> The embryo of the chick is extremely sensitive to selenium toxicity. Hatchability of eggs is reduced by concentrations of selenium in feeds that are too low to produce symptoms of poisoning in other farm animals. Poor hatchability of eggs on farms has therefore proved to be an aid in locating potentially seleniferous areas where alkali disease in cattle, hogs, and horses may occur (Rosenfeld and Beath, 1964). The eggs are fertile, but some produce grossly deformed embryos, characterized by missing eyes and beaks and distorted wings and feet (Carlson et al. 1951; Franke et al. 1936; Franke and Tully, 1935; Gruenwald, 1958). Inherited abnormalities, such as the creeper mutation in hens, exaggerated the developmental malformations caused by selenium (Landauer, 1940). Deformed embryos were also produced by injection of selenite into the air cell of normal fertile eggs of both hens (Franke et al. 1936) and turkeys (Carlson et al. 1951). Kury et al. (1967) suggested that if the definition of teratogenic effects is expanded to include more than dead or grossly abnormal embryos, the adverse effects of raising chickens on seleniferous soils could be more widespread than has been realized. This conclusion is based on their findings of anemia (low red-blood-cell counts and hemoglobin values) in grossly normal as well as malformed embryos of chicks following injections of seleneous acid into fertilized hen's eggs.
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> The consumption of seleniferous diets interfered with the normal development of the embryo in many mammalian species, including rats (Franke and Potter, 1935; Rosenfeld and Beath, 1964), pigs (Wahlstrom and Olson, 1959), sheep (Rosenfeld and Beath, 1964), and cattle (Dinkel et al. 1963). In sheep, malformations of the eyes and of the joints of the extremities have been reported. The latter cause deformed legs and paired locomotion (Rosenfeld and Beath, 1964). These malformations were also observed in chicks. Holmberg and Ferm (1969), however, did not observe teratogenic or embryotoxic effects in hamsters after intravenous administration of near-lethal doses of sodium selenite.

Robertson (1970) suggested that selenium may be a teratogen in man. Reports in the older literature of the people in Colombia eating toxic grains referred to malformed babies born to Indian women (Rosenfeld and Beath, 1964). Robertson gathered information on the possible association between abnormal pregnancies and the exposure of women to selenite. Out of one possible pregnancy and four certain pregnancies among women exposed to selenite, only one pregnancy went to term, and the infant showed bilateral clubfoot. Of the other pregnancies, two could have been terminated because of other clinical factors. Shamberger (1971) cautions against using the inverse relationship between neonatal deaths and the level of selenium in some parts of the United States as a basis for a conclusion concerning the role of selenium in teratogenicity in human beings. Because of the many other factors in our environment that could influence the biological availability of selenium, it appears that we would be unjustified in concluding, solely on the basis of this evidence, that selenium has no bearing on teratogenicity in human beings. Rosenfeld and Beath (1964) emphasized that studies of mammalian malformations in relation to the age of the embryo or fetus and its susceptibility to selenium would be of great value to basic as well as applied research.

Carcinogenicity. Since the 1940's numerous research studies have demonstrated the toxicity of organic and inorganic selenium compounds to humans and domestic and laboratory animals. Most of the toxicologic projects have investigated the effects of acute and chronic exposures over periods of time significantly less than a lifetime. These studies have failed to demonstrate a significant increase in malignant tumor rates among the selenium exposed animals versus controls not exposed to selenium. Only six long term toxicologic research projects provide information concerning the carcinogenic potential of selenium compounds. The studies can be summarized as follows:

Nelson, et al. (1943). The study was designed to determine the lower level of selenium necessary to produce chronic toxicity. Seven groups of 18 female rats each (inbred Osborne Mendel strain) were fed selenium in organic combination in corn and wheat and in a mixed inorganic selenide (a solution of ammonium potassium sulfide and ammonium potassium selenide, containing 48 gm of Se per liter of solution) beginning at 3 weeks of age at levels of 5, 7, and 10 µg/g of diet. Mortality was high and found to be approximately proportional to the level of dietary selenium (Table 6). One-hundred-and-twenty-six rats

were divided into 7 groups of 18. Only 53 survived 18 months; 39 survived 24 months. Of the 53 rats that survived 18 months, 11 developed liver tumors diagnosed as hepatic cell adenomas or low grade hepatic cell carcinomas, and four others had pronounced adenomatoid hepatic cell hyperplasia that could be interpreted as a transition to tumor. In the 73 rats that died, or were sacrificed before 18 months, there were no tumors and no advanced adenomatoid hyperplasia, although cirrhosis was fairly frequent (after 3 months). The 14 control rats that lived at least 18 months had neither adenomatous and neoplastic lesions nor cirrhosis. The spontaneous incidence of hepatic tumors in the colony (source of control animals) at that time was 0.0 percent in rats less than 18 months old, 0.5 percent in rats 18 to 24 months old, and 0.9 percent in rats finishing a two year experimental or control period. None of the tumors in the test animals had metastasized. No tumors occurred in livers that were not cirrhotic. Nelson, et al. (1943) provided this description of the livers and tumors:

> Upon microscopic examination, portions of the peripheries of the tumors were found separated from the rest of the liver by collagenous fibers, but there was no complete encapsulation. The growths were composed of fairly regular to irregular cords of hepatic cells, usually more oxyphilic than the surrounding liver in the adenomas and less oxyphilic in the carcinomas. Some tumors showed no mitoses after several minutes search and in others a few or even a moderate number were seen in a shorter time. Bile duct proliferation was slight except in one instance, where the peripheral 1 to 2 mm of a 3 cm tumor was composed of small bile ducts. Hemosiderin pigmentation and fibrosis within the tumors were not striking; focal necrosis was seen rarely, and hemorrhage not at all. Fatty degeneration was slight and was the same as, or a little less than, in the surrounding liver; the livers of the selenium control rats also showed a slight fatty degeneration which was not found in our other control groups on more adequate diets. A few of the tumors enclosed small foci of myeloid cells, and in a few there were small cystic areas. Since sections were not made of every tumor, some livers listed as showing adenoma may have also contained carcinoma and vice versa.
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> The differentiation between adenoma and low grade carcinoma was difficult to make in this series of tumors; the latter showed greater irregularity of liver cell cords, decreased oxyphilia of liver cells, more mitotic figures, and an invasive tendency at their margins.

Harr, et al. (1967); Tinsley, et al. (1967). The National Cancer Institute funded a contract with the Oregon State University to further investigate the toxicity and carcinogenicity of selenium ions. A total of 1,437 Wistar rats from the University maintained colony were assigned to 34 different dietary groups designed to test the toxic and carcinogenic effects of dietary sodium selenite and sodium selenate (selenium levels ranged from 0.5 to 16 ug/g) in animals maintained on high and low protein basal rations (22 percent casein, 12 percent casein, and 12 percent casein + 0.3 percent DL-methionine). Both male and female rats were included in the experiment but the number of each assigned to the individual dietary groups was not reported. The age of the animals at the time of initial exposure was also not reported, but with the exception of 136 animals that were killed at specific ages, all animals were maintained until death or until moribund at which time they were sacrificed. Since the primary purpose of the study was to evaluate the carcinogenic potential of selenium, a suspect hepatocarcinogen, N-2-fluorenyl-acetamide (FAA) was fed at dietary levels of 100 and 50 ug/g to establish the index of carcinogenesis in the colony. Nine of the dietary groups with a total of 335 animals were used in complementary experiments to test such things as exposure to multiple dose levels, intermittent exposures, and limited feed intake.

Due to excessive losses in the high selenium groups (16 ug/g selenite + 22 percent casein, 16 ug/g selenate + 22 percent casein, and 8 ug/g selenate + 12 percent casein), the animals in these groups were sacrificed early. One-hundred-and-seventy-five rats lived two years or more (Table 7). The rats on the control diets showed no evidence of malnutrition. The hepatic changes of the older animals included accentuated lobular pattern, hyperemia, cellular degeneration, mildly proliferative hepatocytes, double nuclei, and multiple nuclei.

Eleven-hundred-and-twenty-six out of the original 1,437 animals were autopsied.

Acute toxic hepatitis was generally observed in animals receiving selenium added to the semipurified diets at the rate of 4, 6, 8, or 16 µg/g and in the commercial diet with 16 µg/g of added selenium. The typical animal lived less than 100 days. The surface of the liver was mottled with pale-yellow or white areas and the margins of the lobes were stippled with pale foci. Parenchymatous degeneration was present. The cytoplasm of the hepatic cells was finely granular and eosinophilic. Some of the animals suffered from chronic toxic hepatitis. There were three gross variations in the affected livers: (1) small hobnailed surface, (2) irregular mottled surface, and (3) diffusely enlarged liver. Hyperplastic lesions predominated in the livers of about 50 percent of the selenium fed animals which lived more than 282 days.

Sixty-three neoplasms were found in the study (Table 8). Forty-three occurred in the 88 rats fed FAA. The other 20 were randomly distributed through the experimental diets and included no hepatic neoplasms.

Thus, although lifetime exposures to toxic levels of selenium were found by these workers to produce drastic changes in liver and other organs of rats, no hepatic cancers were observed among the selenium exposed animals. The total number of cancers and the site distribution appear similar to that observed in the controls.

Harr, et al. (1967) concluded that neoplasia in the rat are not induced by selenite, by selenate, or by methionine and selenate.

Scott (1973) has provided some discussion concerning the potential causes for the differences in results observed by Nelson, et al. (1943) and Harr, et al. (1967). Some of the possible (based on the available information, it is impossible to conclusively determine the causes for the differences) explanations are:

1. Nelson and associates used the Osborne Mendel strain of rats whereas Harr and associates used the Wistar strain: it is possible that the two strains may have genetic differences that affect the biologic response to selenium.

2. Harr and associates fed sodium selenate or sodium selenite to provide the levels of dietary selenium, whereas the Nelson group used various levels of seleniferous corn and wheat to provide the selenium levels in most of their work. Nelson, et al. (1943) report tumors in two rats which had received 10 ug/g of selenium in a mixture of ammonium potassium sulfide and ammonium potassium selenide. Nelson, et al. (1943) did not feed a control lot ammonium potassium sulfide alone, nor did they have a spectrophotometric analysis of the seleniferous grains to determine whether or not these grains may have been contaminated with a known carcinogen.

3. Nelson et al. (1943) reported hepatomas only in rats that also showed cirrhosis.

4. The hyperplasia and "hobnail" appearance of the livers which Harr and associates observed may have been much more severe in rats already suffering from cirrhosis, thereby forming foci which resembled tumors.

Cherkes, et al. (1962), and Volgarev and Tscherkes (1967). In three series of experiments, they fed selenium as sodium selenate to 200 heterozygous rats at the rate of 4.3 or 8.6 ug/g of feed. The feeds were not semipurified. They contained 12 to 30 percent protein with addition of riboflavin, methionine, atocopherol, cystine, nicotinic acid, and choline in appropriate groups. In the third series, a set of 200 control rats were fed a stock diet, and observed for a longer period of time than the experiment.

In the first series, 40 rats were fed 4.3 ug/g of selenium as sodium selenate plus 12 percent casein in the diet. No indication was given as to the age or weight of the animals at the start of the experiment, but it is

assumed weanling rats were used. In the 23 rats surviving 18 months or longer, 10 developed tumors, and four had precancerous lesions; no information is given concerning the 17 rats that died prior to 18 months. Of these ten, four developed sarcomas, three developed hepatic carcinoma (two with metastases to the lungs), and three had hepatocellular adenomas. Of the 13 noncancerous rats, four had lesions termed precancerous. The lesions were cholangiofibrosis, oval cell (bile duct cell) proliferations, and biliary cysts. There was no indication as to when the tumors appeared other than the statement that they were seen some time after the eighteenth month. No control rats were included in this series.

In the second series, sixty male rats, divided into three groups of 20, were fed 4.3 ug/g of selenium in a 12 percent casein diet for six months, and then subjected to liver biopsy. Group I was maintained on 12 percent casein but the level of selenium was increased to 8.6 ug/g of diet commencing with the seventh month. Group II was fed 8.6 ug/g of selenium in the diet but the casein level of the diet was raised to 30 percent. Group III received the same diet as Group II with the addition of riboflavin. Protein levels in Groups II and III were increased to 30 percent to prevent possible death losses from the increased selenium levels.

The biopsy specimens collected at the end of 6 months showed mild degenerative changes in the liver, but no lesions that could be classified as cancerous or precancerous.

The eighteen surviving rats in Group I at the end of six months died within 6 months following the increase of selenium to 8.6 ug/g of the diet. Microscopic examinations revealed characteristic histologic changes of selenium intoxication. There were no cancerous or precancerous changes in the liver.

Seventeen of the original 20 rats assigned to Group II were surviving at

the end of the initial six month period. Increasing the dietary selenium level from 4.3 µg/g to 8.6 µg/g while also increasing the protein level to 30 percent appeared to have no effect on survival since 16 animals still remained at the end of one year and 12 lived more than two years. At 14 months, sacromas were found in two rats, one of the mediastinum, the other of the mesenteric lymph nodes. A third rat had liver cirrhosis with multiple nodules. No precancerous lesions similar to those in series 1 were found. The rats examined after one year of exposure showed changes characteristic of chronic selenium poisoning. Degenrative and atrophic changes in the liver and spleen were observed in rats surviving two years.

Seventeen of the 20 rats assigned to Group III died within the first year. Of the 3 rats surviving over one year, one developed a sarcoma of the mesenteric lymph nodes that was found at 19 months, another had hyperplasia of the liver cells with some nodules of hepatocellular adenoma, and the third rat had only degenerative changes in visceral organs.

In the third series 100 heterozygous male rats weighing 100 gm each were allocated into five groups of 20 animals each and placed on a basal diet containing 12 percent casein and 4.3 µg/g of sodium selenate.

Additives were included in the group diets in order to test their effects on the development of possible selenium induced carcinogenesis. The assignment of dietary additives was as follows:

Group I : no additives

Group II : methionine at 5000 µg/g and a-toxopherol at 10,000 µg/g

Group III: cystine at 5000 µg/g

Group IV : nicotinic acid at 5 mg per rat per day

Group V : choline at 35 mg per rat per day

All of the rats in Group I were dead by the twenty sixth month, 10 months

shorter than similarly fed animals in series 1. The animals in Groups II, IV, and V were sacrificed at the end of the twenty fifth month and those in Group III at the end of the seventeenth month.

None of the animals possessed tumors or precancerous lesions.

No spontaneous tumors were observed in the 200 heterozygous male control rats fed stock ration.

Volgarev and Tscherkes (1967) have suggested that the reason for the difference in tumor rates between the series 1 and series 3 may be explained by the fact that the experiments of series 3 were started two years later than series 1 and involved animals obtained from a different source. They note, however, that of 10,000 other rats used in their laboratory, not a single case of spontaneous liver cancer was seen. No information is provided concerning the examination methods, exposures, rat species, etc. for the 10,000 rats.

According to Van Houwilling (1973), it has been discovered that the rats used in the first two series were infected with a parasite which is known to induce tumors; the specific parasite was not named. Hence, the results of this experiment are difficult to interpret.

Schroeder (1967) and Schroeder and Mitchener (1971 and 1972). Four-hundred-and-eighteen weanling rats of the Long-Evans strain (BLU:(LE)) born from random-bred females (purchased from Blue Spruce Farms, Altamont, N. Y.) were fed a diet of whole rye flour (60 percent), dry skim milk (30 percent), corn oil (9 percent), iodized sodium chloride (1 percent), to which were added vitamins and iron. The rats were divided into four groups of approximately 100 animals each. One group served as a control, and the second, third, and fourth groups received 2 to 3 mg/l of sodium selenate, sodium selenite, and 2 mg/l of tellurite in the drinking water. Within a group, the results are reported separately by sex. Because selenite was very toxic to male rats, causing 50 percent mortality in 58 days, sodium selenate was substituted at 2

mg/l until one year of age when the level was raised to 3 mg/l. There were no significant differences in the weights of male rats fed selenate and their controls at any interval up to 36 months of age. Since selenite was not as toxic for females (50 percent mortality at 348 days), sodium selenite was not substitued for selenite and the dose level continued at 2 mg/l.

The diet contained approximately 24 percent protein, 65 percent carbohydrate, and 11 percent fat on a dry basis, at 396 kcal/100 g. Selenium content of the diet was 0.05 µg/g, wet weight.

When the rats were 21 months old, an epidemic of virulent pneumonia struck the colony with considerable loss of life. It was controlled with penicillin in drinking water in about 3 weeks' time. Losses in the various groups were as follows (percent): Male controls 36.5, selenate 48.9; female controls 27.2, selenate 14.8.

The average weights of male and female groups of selenium-supplemented rats were 3 to 7 percent heavier than the corresponding nonsupplemented control groups for each six month age period after 1 year of age except for males at 18 months (controls were 1.7 percent heavier).

Approximately 75 percent of the control and selenate animals living prior to the epidemic of pneumonia at 28 months were autopsied. Histological examinations were performed on 65 control and 48 of the selenate exposed rats. The criteria used to select animals for autopsy or histologic examination was not reported. Ages of animals at autopsy are not provided.

Eleven malignant tumors were found in the control animals and 20 were reported in the selenate-supplemented animals. The types of tumors and the numbers were given as follows:

Tumor Type	Control Group	Selenate Group
Mammary	5	3
Spindle cell sarcoma	2	4
Leukemia types	2	4
Pleomorphic carcinoma	1	2
Leiomyosarcoma	1	
Malignant hamartomas		2
Undifferentiated sarcoma		1
Round cell sarcoma		1
Malignant glioma		1
Ovarian adenocarcinoma		1
Spindle cell sarcoma invading the heart		1
	11	20

The anatomical locations of the sarcomas and pleomorphic carcinomas were not reported. These tumors may have been sclerosed granulomas secondary to the epidemic of pneumonia. Histologic slides were prepared only from selected organs and animals, and the rationale for that selection was not reported. Since the organs and tissues were not systematically searched, type and incidence of histologic lesions are not known (National Research Council, 1976). No information concerning types and numbers of tumors by sex within groups is reported.

Malignant tumors in the selenite-fed rats included a reticulum cell sarcoma, and three spindle cell sarcomas invading the heart.

Very little malignant tumor information is given concerning the male and female groups initially fed selenite. Due to the toxicity of selenite the exposure for males was changed to selenate and both groups were sacrificed prior to the age of high tumor incidence.

Schroeder and Mitchener (1972) repeated the rat studies in mice. Here, treatment with 3 mg/l of selenium via the drinking water did not have a significant effect on the incidence of spontaneous tumors.

National Cancer Institute (1978). During June of 1978, the U.S. Environmental Protection Agency received a copy of the data sheets for a National Cancer Institute supported bioassay study of selenium disulfide conducted at Hazleton Laboratories (NCI contract 702209). No formal writeup with project description, interpretation, or conclusions was received.

Eight groups (four female and four male) of mice (stock/strain B6C3F1) were included in the lifetime bioassay study; each group contained 50 animals. The four groups for each sex were defined as follows: untreated control (animals live in same environment and fed similar diet to treated animals but do not receive anything by gavage), vehicle control (animals live in same environment and fed similar diet to treated animals but receive the vehicle-cellulose, carboxymethyl-by gavage), low dose test (20 mg/kg of selenium disulfide, or 11.05 mg/kg of selenium) and high dose test (100 mg/kg of selenium disulfide, or 55.24 mg/kg of selenium). Oral administration was initiated about 2 months after birth and continued once daily for the remainder of life (up to 728 days).

From the raw data sheets it is apparent that the employed mice strain has a high rate of spontaneous tumors of multiple anatomic sites (Table 9). For male mice, the malignant tumor incidence for the selenium disulfide exposed groups is not significantly different from the control groups (Table 9); no significant differences were observed for specific anatomic sites or for the animals as a whole. However, the high dose female group has significantly more animals with hepatocellular carcinoma (21 out of 49 animals, or 43 percent) than the two control groups (2 out of 50, or 4 percent for untreated controls and 0 out of 49 for vehicle controls). No other significant differences were

observed for the females.

This experiment demonstrates that at least in females, selenium disulfide is a carcinogen.

Since selenium disulfide is not just another salt of selenium, but instead a separate and distinct compound it cannot be assumed that these results show that inorganic selenium (selenite or selenate) compounds are carcinogenic. Clearly, similar bioassays are needed for inorganic selenium compounds.

From the studies just cited, it is apparent that the question concerning carcinogenicity of inorganic selenium has not been answered and will not be until several specifically designed lifetime bioassay studies are performed. Sufficient research has been completed to raise the possibility that inorganic selenium is a carcinogen, but none of the present studies produces a weight of evidence or conclusive dose response data for risk estimation. The Commissioner of the Food and Drug Administration has concluded that: (1) The available information does not support classification of selenium or its compounds as having carcinogenic activity, (2) the use of selenium as set forth by the Food and Drug Administration regulations constitutes no carcinogenic risks (Food and Drug Administration, 1973). The conclusions of the National Academy of Science (1976) report on selenium are:

> Despite an initial report of selenium as a carcinogen (Nelson et al. 1943), chronic experimental exposure of rats and mice to selenium salts over a period of 12 years has not induced neoplasia (Cherkes et al. 1962; Harr et al. 1967; Nelson et al. 1943; Schroeder, 1967; Schroeder and Mitchener, 1972; Schroeder and Mitchener, 1971; Shamberger and Frost, 1969; Tinsley et al. 1967; Volgarev and Tscherkes, 1967). During the same period, selenium salts have been used prophylactically and therapeutically in ruminants, omnivores, and carnivores throughout the world. Epidemiologic and demographic evidence from the widespread use of selenium supplementation, exposure to toxic concentrations of selenium in feeds, and use of selenium in shampoos and industrial plants, does not suggest that selenium is carcinogenic; rather, it may be correlated with a reduction in the evidence of human and ovine cancer (Frost, 1971; Schroeder and Mitchener, 1972; Selenium and cancer, 1970; Shamberger and Rudolph, 1966; Shamberger et al. 1973; Shamberger, et al. 1972; Shamberger and Willis, 1971; Wedderburn, 1972).

The conclusion of the International Agency for Research on Cancer is that the available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds. The available human data provide no suggestion that selenium is carcinogenic in man, and the evidence for a negative correlation between regional cancer death rates and selenium is not convincing (IARC Monograph, 1975).

It seems that the EPA must also conclude that there are not sufficient and adequate data to determine if selenium compounds are carcinogenic.

Anticarcinogenesis. The National Research Council (1976) at the request of and funded by the U.S. Environmental Protection Agency under contract no. 68-02-1226 has thoroughly summarized and reviewed the literature concerning the anticarcinogenic effects of exposure to selenium compounds. Hence the material in this section is quoted from that review.

> The demonstration of the relationship of selenium to human cancer is limited to demographic studies and comparisons of blood levels of selenium in patients with and without malignancies. However, Weisberger and Suhrland (1956) discussed the effect of selenium cystine on leukemia, and Chu and Davidson (1972) listed selenium compounds among potential antitumor agents.
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> Demographic and experimental observations of Shamberger and associates support the concept of pharmacologic and medical uses of selenium salts (Schrauzer and Rhead, 1971; Shamberger and Frost, 1969; Shamberger et al. 1973; Shamberger and Willis, 1971). They found an inverse correlation between the incidence of cancer deaths, the concentration of selenium in the patients serum, and geographic incidence of selenium--low, moderate, or high. The concentration of selenium in the blood of cancer patients averaged 74 percent of normal. However, the blood of patients with some forms of cancer contained normal concentrations of selenium.
>
> The selenium contents of diets of 17 paired human males with and without gastric cancer were compared and related to dietary antioxidants and food preservatives (Shamberger et al. 1972). Patients with gastrointestinal cancer or metastases to gastrointestinal organs had significantly lower levels of selenium in the blood than normal patients (Shamberger et al. 1972). o elevations of selenium in the blood of cancer patients were noted. The authors postulated that selenium acted to prevent attachment of the carcinogen to DNA sites.
>
> Solymosi (1963) also reported on the effect of adding sodium selenide to cancer-inducing preparations of anthracene compounds or adding sodium

selenite to the feed of rats exposed to anthracene compounds. Rats fed dietary selenite, and those treated with preparations of anthracene compounds with added selenide, developed fewer skin papillomas than rats treated with anthracene compounds without added selenide.

Harr et al. (1972) reported that after 200 days of feeding selenium-depleted rats a semipurified feed containing 100 ng of the hepatic carcinogen FAA per gram of feed and 0.1, 0.5, or 2.5 µg of added selenium as selenite per gram, the incidence of mammary and hepatic neoplasia with or without 0.1 µg of added selenium per gram was three times greater than the incidence in rats supplemented with 0.5 or 2.5 µg of selenium per gram. The low-selenium groups (0 and 0.1 µg/g died before 200 days of age and had a 90 percent incidence of neoplasia. At this time, 35 percent of the rats fed 0.5 and 2.5 µg of selenium per gram had died, and the incidence of neoplasma was 30 percent. Most of the remaining rats fed 0.5 and 2.5 µg of selenium per gram lived for an additional 120 days. By this time, they had received the carcinogen for an additional 120 days, and the total incidence of neoplasma was 90 percent, as observed in the groups receiving 0 and 0.1 µg of selenium per gram. Since the longevity of the rats was proportional to the amount of selenium supplementation and the duration of exposure to the carcinogen, the increase in cancer in the rats, heavily supplemented with selenium, may have been due to greater exposure to the carcinogen or to longer time for induction.

The mammary tumors in the group not supplemented with selenium were more invasive than those in rats from the three supplemented groups and predominated in the pelvic rather than in the thoracic region, as in the selenium-supplemented or commercially fed rats.

Johnston (1974) studied the effect of selenium on the induction of cancer by FAA and diethylnitrosamine in selenium-depleted rats over a restricted exposure period. Because of widely varying rates of feed consumption by the principal and control groups and the high incidence of neoplasia in all the exposed groups, results were confusing.

Jacobs et al. (1977) studied the effect of 4 mg/l sodium selenite supplemented drinking water available ad libitum on the incidence of colon cancers in rats induced by DMH (1, 2-Dimethylhydrozine) or MAM (Methylazoxymethanol acetate). Rats receiving DMH and no selenium exhibited 87 percent tumor incidence (13 out of 15 rats had tumors). Selenium significantly (P=0.025) decreased the incidence of colon tumors induced by DMH such that only 6 out of 15 rats had no tumors. No significant difference in tumor incidence was apparent between groups receiving MAM with or without selenium supplements.

The unique ability of selenium to reduce methylene blue was reported by Schrauzer and Rhead (1971), who suggested that this ability might provide a

basis for testing for cancer or susceptibility thereto. Clayton and Baumann (1949) have reported on the relation between diet and azo dye tumors. In studies of lipid therapy, based on the types of lipid imbalance in cancer patients, Revici (1955) reported that the most satisfactory and reproducible palliative effects were obtained by using synthetic lipids containing bivalent selenium, a seredipitously acquired observation alluded to be Frost (1971). Berenshtein and Aleshki (1968) have described the effect of selenium on lipid metabolism.

CRITERION FORMULATION

Existing Guidelines and Standards

In 1942, the U.S. Public Health Service (Public Health Service, 1962; McDermott, 1973) established 50 µg/l as the maximum level of selenium permissible in the finished water of Interstate Carrier water supply systems. When the standards were re-evaluated and revised in 1962, the maximum permissible level was reduced to 10 µg/l (Public Health Service, 1962). The U.S. Environmental Protection Agency (1975b) has established the 0.01 mg/l limit as part of the U.S. Environmental Protection Agency National Interim Primary Drinking Water Regulations that went into effect in June of 1977. According to the Safe Drinking Water Act (U.S. EPA, 1974) this level now applies to all utilities that serve 25 persons and/or have 15 service connections.

The Threshold Limit Value (TLV) set for the time-weighted average concentrations of selenium in air for a normal 8-hour work day or 40-hour workweek is 0.2 mg/m^3 (Am. Conf. Gov. Ind. Hyg., 1977).

The Food and Drug Administration (1973) has ruled that sodium selenite or sodium selenate may be added to the complete feed for swine and chickens up to 16 weeks of age at a level not to exceed 0.1 µg/g, and for turkeys not to exceed 0.2 µg/g.

Current Levels of Exposure

It is estimated that the average adult intake of selenium is roughly 130 to 150 µg of selenium each day from food

(Watkinson, 1974; Schroeder, 1970). However, it is well known that the level of selenium in food is very dependent on the amounts in the soil and water where the food is grown or in the feeds that the livestock eat (Levander, 1976). The range of levels for specific vegetables grown in non-seleniferous versus seleniferous areas are: potato (0.005 to 0.940 μg/gram), tomato (0.005 to 1.22 μg/gram), carrots (0.022 to 1.30 μg/gram), cabbage (0.022 to 4.52 μg/gram),and onion (0.015 to 17.8 μg/gram) (Levander, 1976). Hence, persons living in areas where the selenium content of the soils is high will likely be exposed to daily dietary levels above 150 μg. Levander (1976) has estimated that an average 6-month-old infant consumes 28 μg of selenium per day from food.

Levels of air selenium in municipalities and communities range from 0.0025 $\mu g/m^3$ to 0.0097 $\mu g/m^3$ (Dams, et al. 1970; Harrison, et al. 1971; Pillay, et al. 1971). Assuming average total daily inhaled volumes of 21.2, 11.1, and 1.4 cubic meters for men, women and infants (0 to 11 weeks of age), the estimated ranges of daily selenium exposures from ambient air are 0.053 to 0.206 μg, 0.028 to 0.108 μg, 0.004 to 0.014 μg, respectively; estimated volumes of inhaled air are based on time-weighted averages of Tidal Volumes and Respiratory Frequencies (CIBA GEIGY Limited, 1970). Clearly, selenium in ambient air does not contribute significantly to the overall selenium exposure level of the general population. Levels of exposure from use of selenium based shampoos are unknown.

Special Groups at Risk

Since selenium toxicity depends on levels of nutrition and exposure to other synergistic and antagonistic elements (Levander, 1971), it would be expected that some individuals are at greater risk than others due to dietary differences.

Basis and Derivation of Criterion

The question of the carcinogenic potential for ingested selenium has been reviewed in recent years by the National Academy of Sciences while studies by the National Cancer Institute (1978) have added new but inconclusive evidence to the issue. The Academy (National Research Council, 1977) states that although the 1962 drinking water standard was recommended at 10 ng/l because of evidence that selenium was carcinogenic in animal studies, "a current literature review of animal studies does not support this contention."

An NCI bioassay of selenium disulfide at 100 mg per kilogram (equivalent to 400 ppm of selenium alone) has reported the induction of hepatocellular carcinomas in female mice. This is consistent with an earlier report by Nelson, et al. (1942) that seleniferous grains and ammonium potassium selenide at 10 ppm induced liver tumors in rats. However, several inconclusive and negative carcinogenesis studies of selenite and selenate compounds ranging from 2-15 ppm have been reported since Nelson's work.

The carcinogenicity of selenium compounds is a complex issue because: (1) there is evidence that selenates, selenites, and selenides at non-toxic levels inhibit the development of spontaneous tumors, protect against the induction of

tumors by known carcinogens, counteract the promotion of tumors in mouse skin initiator-promotor experiments, and inhibit the mutagenic action of chemicals in bacteria; (2) human cancer mortality at several organ sites appears to be negatively correlated with estimated selenium dietary intake and blood selenium levels, according to a tabulation of data from several countries; (3) even at moderate concentrations (5-10 ppm) of selenates and selenites the chronic toxicity is high, and this toxicity interferes with the development of tumors because of early deaths; (4) the aqueous solubility and therefore the availability of different selenium compounds for absorption from the GI tract is markedly variable; (5) low concentrations of selenium (0.01 to 0.1 ppm in the diet) appear to be nutritionally essential; and (6) the reports of the chronic toxicity studies are difficult to compare because of the large number of different selenium compounds studies, the dependence of tumor induction on changes in protein and selenium levels in the diet and the incomplete histopathological examination performed in many of the available studies.

For these reasons it does not seem reasonable to use carcinogenic toxicity and risk as a basis for health criteria without additional research.

Obviously, one of the major factors involved in estimation of the minimum dose of selenium required to produce chronic toxicity in man or animals is the criteria, or definition, of chronic toxicity. The National Research Council (1976) has reviewed the literature in an attempt to establish a

"no-effect" dose level for selenium and thus arrive at some conclusion concerning the level in water that can be expected to injure man. From this review, they found that the growth rate for rats fed a normal diet was inhibited if exposed to 4 to 5 μg/l of selenium in the diet. Only 1 μg/g of selenium in the diet was required to reduce growth in rats fed a diet severely deficient in vitamin E. Hadjimarkos (1971) has demonstrated in rats that selenium added to drinking water at a level as low as 2.3 mg/l during tooth development increases the incidence of caries. The National Research Council (1976) suggests that if histopathologic observations are used as the criteria for chronic toxicity that 1 μg/g of selenium in the diet of 1 mg/l of selenium in drinking water may be shown to be sufficient to produce toxicity. However, it is recognized that the physiologic significance of the findings may not be clear, and the same may be said for biochemical parameters indicating that even lower levels can be toxic.

The amount of selenium needed to prevent deficiency diseases in animals is very small; 0.1 μg/g in the diet is a nutritional adequate level for most species. Such a level translates into a human requirement of about 60 to 120 micrograms per day depending on the biologic availability in the diet, a person's physiologic status with regard to other nutrients, and other factors (Jour. Am. Dietetic Assc., 1977; Levander, 1976).

It is estimated that on the average, adults intake roughly 130 to 150 μg of selenium per day from food (Watkinson, 1974; Schroeder, et al. 1970). Levander (1976) has estimated

that an average 6-month-old infant consumes 28 μg of selenium per day from food.

The uneven distribution of selenium in the soils of the United States could conceivably cause persons living in low-selenium areas and consuming only locally produced foods to develop a low-selenium state, just as some who live in high-selenium areas may ingest excess selenium. However, most nutritional authorities agree that there is currently no evidence of selenium deficiency in human populations in the United States, probably because of interregional food shipment that characterizes our present-day food supply (Jour. Am. Dieteric Assc., 1977; Levander, 1976). Hence, there is no need to use water as a vehicle for supplementing the diets of the general population.

In consideration of the probable importance selenium plays in the human diet, and the varied but definite exposure potential from food intake, drinking water and other sources, the strategy for identifying a criterion level for ambient waters must be based on minimizing the likelihood of contributing a sufficient amount of selenium that would increase an average total exposure above a selected toxic level.

The growth inhibition with vitamin E deficiency would be the candidate of first choice for toxicity effect and extrapolation into human effects. However, the vitamin E circumstance would be a special situation for the average population and therefore the increased incidence of dental caries at 2.3 mg/l becomes the targeted effect for extrapolation to humans.

If it is assumed that rats consume 10 percent of their body weight per day during their growth period, the toxic effect (incidence of dental caries) is demonstrated at levels of selenium as low as 16.1 mg selenium intake per day.

$$2.3 \frac{mg}{l} \text{ selenium} = 2.3 \frac{mg}{kg} \text{ feed}$$

Assuming 300gm rat:

$$\text{feed intake} = 2.3 \frac{mg}{kg} \times 10\% \text{ (300gm)} = \frac{69 \times 10^{-3} \text{mg Se}}{\text{day}}$$

$$\text{animal dose} = \frac{69 \times 10^{-3} \text{mg}}{\frac{\text{day}}{300\text{gm}}} = \frac{0.23 \text{ mg Se}}{\text{kg body wt}}$$

$$\text{equivalent human dose} = \frac{0.23 \text{ mg Se}}{\text{kg body wt}} \times 70 \text{ kg man} = 16.1 \text{ mg Se}$$

Thus, the equivalent human dose for incidence of dental caries is $16.1 \frac{\text{mg Se}}{\text{day}}$

For comparison purposes a similar calculation for the growth inhibition under vitamin E deficiency is $\frac{7 \text{ mg Se}}{\text{day}}$

In summary, the minimum toxic daily dose is 16,100 micrograms and the average daily dietary intake is 130 to 150 micrograms leaving a difference of 15,950 micrograms. Populations living in seleniferous areas may be exposed to much higher levels of selenium both in the food and water. Since little is known concerning the minimum toxic dose in humans and there is uncertainty about the carcinogenic potential of Se, it does not seem reasonable to permit the level in

water to be more than ten to twenty percent of the dietary level. If the maximum water contribution is set at 13 to 30.0 micrograms per day, the total level (dietary and water) will be well below the estimated minimum toxic dose. Assuming that the average individual consumes 2 liters of drinking water per day, 18.7 grams of fish, and that the bioaccumulation factor for fish is 18, the estimated level for water is calculated as follows:

$$\text{Criterion Level} = \frac{13}{2 + (0.0187)\ 18} = 5.56\ \mu g/\text{liter}$$

$$\text{or} = \frac{30.0}{2 + (0.0187)\ 18} = 12.84\ \mu g/\text{liter}$$

Based on these calculations it appears that the U.S. Environmental Protection Agency Drinking Water Standard of 10 µg/liter is probably an appropriate ambient criterion level to protect the health of the U.S. population.

Table 1. Selenium Content of Some Foods in the American Diet
(Morris and Levander, 1970)

Food	Average Selenium Content µg/g (wet wt.)
Vegetables, canned and fresh[1]	0.010 (0.004-0.039)
Fresh garlic	0.249
Mushrooms, canned and fresh	0.118
Fruits, canned and fresh	0.006 (<0.002-0.013)
Cereal products[2]	0.387(0.0266-0.665)
Corn flakes	0.026
Rice cereal	0.028
Egg white	0.051
Egg yolk	0.183
Brown sugar	0.011
White sugar	0.003
Cheeses	0.082 (0.052-0.105)
Table cream	0.006
Whole milk	0.012
Meat (excluding kidney)	0.224 (0.116-0.432)
Seafood	0.532 (0.337-0.658)

[1]Mean excluding mushroom and garlic

[2]Mean excluding corn flakes and rice cereal

Table 2. Selenium content of seleniferous vs. non-seleniferous vegetables (µg Se/gram wet weight)

Product	Non-Seleniferous[1] Morris & Levander (1970)	Seleniferous[2] Smith & Westfall (1937)
Potato	0.005	0.940
Tomato	0.005	1.22
Carrots	0.022	1.30
Cabbage	0.022	4.52
Onion	0.015	17.8

[1]Samples were purchased in the Beltsville, Maryland, area from local food stores. Brand name products were selected whenever possible.

[2]Samples of foodstuffs used by the people living in four seleniferous counties (Tyman, Tripp and Gregory in South Dakota and Boyd in Nebraska) were collected and analyzed for selenium content.

Table 3. Estimated human daily intake of selenium from dietary sources (µg/day)

Food	New Zealand[1]	Maryland, U.S.A.[1]	Canada[1] (Ontario)	Canada[2] Toronto	Canada[2] Toronto	Canada[2] Winnipeg	Canada[2] Halifax	Japan
Plant								
Vegetables Fruit, Sugars	5.8	5.4	6.9	5.1	1.3	9.1	7.4	6.5
Cereals	4.3	44.5	74.4	62.0	111.8	79.8	105.0	23.9
Animal								
Dairy products	8.4	13.5	23.4	6.5	5.0	27.6	21.8	2.3
Meat, fish	37.7	68.6	46.0	24.7	30.4	64.3	90.0	55.6
Totals	56.2	132.0	150.7	98.3	148.5	190.8	224.2	88.3

[1] Watkinson (1974)

[2] Thomson et al. (1975)

[3] Sakurai and Tsuchiya (1975).

Table 4. Estimated infant daily intake of selenium from dietary sources (6-month old, 15 pound child) (Levaner, 1976)

Food	Daily Consumption grams	µg Se/gram	Daily Intake µg Se
Milk	824	0.013[1]	11
Orange	122	0.014[1]	2
Dry Mixed Cereal	10	0.540[2]	5
Egg Yolk	17	0.437[1]	7
Strained Meat	28	0.097[1]	3
Strained Fruit	57	0.002[1]	-
Strained Vegetable	57	0.003[1]	-
Total Selenium Intake			28

[1]Average of Morris & Levander (1970) and Arthur (1972)

[2]Arthur (1972)

Table 5. Acute toxicity of some selenium compounds (National Research Council, 1976)

Compound	Experimental Animal	Mode of Administration	Toxicity	Reference
Sodium selenite	Rat	Intraperitoneal injection	MLD[b,d,g-3.50] 3.25 mg Se/kg body wt	Franke & Moxon, 1936
	Rat	Intravenous injection	MLD[c,g] 3 mg Se/kg body wt	Smith & Westfall, 1937
	Rabbit	Intravenous injection	MLD[c,g] 1.5 mg Se/kg body wt	Smith & Westfall, 1937
	Rat	Injection	MLD[d,g] 3-5.7 mg Se/kg body wt	Moxon & Rhian, 1943
	Rabbit	Injection	MLD[d,g] 0.9-1.5 mg Se/kg body wt	Moxon & Rhian, 1943
	Dog	Intraperitoneal injection	MLD[d,g] 2.0 mg Se/kg body wt	Moxon & Rhian, 1943
Sodium selenate	Rat	Intraperitoneal injection	MLD[b,g] 5.25-5.75 mg Se/kg body wt	Franke & Moxon, 1936
	Rat	Intravenous injection	MLD[c,g] 3 mg Se/kg body wt	Smith & Westfall, 1937
	Rabbit	Application to skin	83[g] mg of compound caused death in 5 hr; 4[g] mg caused death in 24 hr.	Dudley, 1938
Hydrogen selenide	Rat	In air	All animals exposed to 0.02 mg/liter to air for 60 min. died with 25 days	Dudley, 1938
DL-selenocystine	Rat	Intraperitoneal injection	MLD[a,b,g] 4.0 mg Se/kg body wt	Moxon, 1940
DL-selenomethionine	Rat	Intraperitoneal injection	MLD[a,g] 4.25 mg Se/kg body wt	Klug et al. 1949
Diselenodipropionic	Rat	Intraperitoneal injection	LD_{50}[g] 25030 mg Se/kg body wt	Moxon et al. 1938
Dimethyl selenide	Rat	Intraperitoneal injection	LD_{50}[e,g] 1,600 mg/kg body wt	McConnell & Portman, 1952
Trimethylselenonium chloride	Rat	Intraperitoneal injection	LD_{50}[b,g] 49.4 mg Se/kg body wt	Obermeyer et al. 1971

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Table 5: Continued

[a]MLD, minimum lethal dose; LD_{50}, dose causing death in one-half of test animals.

[b]Smallest amount that would kill 75 percent of the rats in less than 2 days.

[c]Smallest amount that would kill 40-50 percent of the animals.

[d]MLD, minimum lethal dose (single one time dose).

[e]Death within 24 hours after injection was used as the criterion to determine the LD_{50}.

[f]Death within 4 hours after injection was used as the criterion to determine the LD_{50}.

[g]single dose.

[h]60 minutes exposure period.

Table 6. Death and survival information for Nelson et al. (1943) study

Level of Selenium	Number of Deaths by Time Period (Months) 3 or less	3 1/2 to 11 1/2	12 to 17 1/2	18 to 23 1/2	Number of Survivors at End of 24 Months	Number of Rats in Each Group at Beginning of Experiment
5 µg/g (corn)	2	1	5	1	9	18
5 µg/g (wheat)	0	1	3	4	10	18
7 µg/g (corn)	7	0	1	3	7	18
7 µg/g (wheat)	9	2	3	1	3	18
10 µg/g (corn)	13	0	0	2	3	18
10 µg/g (wheat)	12	1	2	2	1	18
10 µg/g (selenide)	2	6	3	1	6	18
Total Experimental	45	11	17	14	39	126
Control	0	2	2	2	12	18

Table 7. Rats living two years
(Harr et al. 1967)

Dietary Selenium Level (µg/g)	Oxidation State	Casein (percent)	Total Number on Diet	Number Living Two Years
0	-	22	110	24
0.5	selenite	22	55	17
2.0	selenite	22	54	14
0.5	selenate	22	56	11
2.0	selenate	22	55	11
0	-	12	109	29
0.5	selenate	12	55	12
2.0	selenate	12	54	6
0	-	12 (added 0.3 percent DL-methionine)	34	10
4	selenate	12	53	1
Commercial Diet	-		55	13
8 (fed alternate weeks)	selenate	22	40	14
4 (fed alternate weeks)	selenate	12	40	13
		Totals	770	175

Table 8. Distribution of neoplasms in experimental diets (Harr et al. 1967)

Diet			Neoplasms				
					Age		
Type	Selenium (µg/g)	No. Necropsies	No.	Type	Low	Medium	High
Selenite with 22 percent casein	0.5	49	1	Uterine Polyp	-	752	-
			11	Lipoma	-	450	-
	2.0	47	1	Mammary Cancer	-	174	-
	6.0, 8.0, 16.0	65	-	-	-	-	-
Selenate with 22 percent casein	0.5	44	1	Uterine Cancer	-	380	-
	2.0	41	1	Lymphoma	-	563	-
			1	Fibroma	-	500	-
	8.0	37	1	Urinary Cancer	-	43	-
	4.0, 6.0, 16.0	54	-	-	-	-	-
Selenate with 12 percent casein	0.5	47	1	Mammary Cancer	-	722	-
			1	Lymphoma	-	730	-
	2.0, 4.0, 6.0, 8.0	103	-	-	-	-	-
Selenate with methionine	4.0	38	-	-	-	-	-
	6.0	13	-	-	-	-	-
	8.0	15	-	-	-	-	-
FAA 100 µg/g 22 percent casein	0	45	12	Hepatic Cancer	243	313	512
			7	Mammary Cancer	243	308	578
			3	Lymphoma	154	247	282

Table 8: Continued

Diet			Neoplasms				
					Age		
Type	Selenium (µg/g)	No. Necropsies	No.	Type	Low	Medium	High
Controls:							
12 percent casein	0	98	3	Mammary Cancer	92	548	707
			1	Lymphoma	-	356	-
			1	Lipoma	-	731	-
22 percent casein	0	103	3	Mammary Cancer	620	678	731
			1	Fibroma	-	458	-
12 percent casein + 0.3 percent DL-methionine		29	1	Broncho Cancer	-	434	-
Commercial diet		46	1	Lymphoma	-	578	-
Variable Selenium and control diets		206	-	-	-	-	-

Table 9. Tumor incidence for rats exposed to selenium disulfide (National Cancer Institute, 1978)

Anatomic Site	Untreated Controls		Vehicle Controls		Low Dose (11.05 mg/kg)		High Dose (55.24 mg/kg)	
	Males	Females	Males	Females	Males	Females	Males	Females
Integumentary System	7[a](49)[b]	1(50)	5(50)	1(49)	8(50)	1(50)	1(50)	1(49)
Respiratory System (Lung)	(49)	(50)	(50)	(49)	(50)	(50)	(50)	(49)
Adenocarcinoma, Nos, Metastic	0	0	0	0	1	0	0	1
Alveolar/Bronchiolar Adenoma	8	2	3	0	8	2	11	8
Alveolar/Bronchiolar Carcinoma	1	0	1	0	2	1	2	4
Other	3	0	5	0	3	0	3	0
Hematopoietic System								
Multiple Organs	6(49)	17(50)	4(50)	17(50)	12(50)	23(50)	8(50)	17(50)
Spleen	0(49)	0(50)	2(50)	0(49)	1(50)	1(50)	1(50)	3(49)
Mesenteric L. Node	0(49)	1(48)	0(50)	0(48)	0(49)	0(50)	1(50)	1(48)
Other	1(49)	-	1(22)	-	1(19)	-	0(19-50)	-
Digestive System								
Salivary Gland								
Adenocarcinoma, Nos	none	0(50)	none	0(46)	none	0(50)	none	1(49)
Liver	(49)	(50)	(50)	(49)	(50)	(50)	(50)	(49)
Hepatocellular Adenoma	2	1	0	0	3	1	0	6
Hepatocellular Carcinoma	17	2	15	0	11	1	23	21
Hemangiosarcoma	0	0	2	0	1	1	1	0
Other	0	0	0	0	1	0	1	0
Pancreas	0(49)	1(50)	1(50)	0(49)	1(50)	0(50)	0(50)	0(49)
Stomach	1(49)	1(50)	1(49)	0(49)	0(49)	1(50)	0(48)	0(49)
Other	0(49)	1(50)	1(49)	0(49)	0(49)	1(50)	0(48)	0(49)
Urinary System	0(49)	none	1(50)	none	0(49)	none	1(50)	none
Circulatory System	0(49)	none	1(50)	none	0(50)	none	0(50)	none

Table 9: Continued

(National Cancer Institute, 1978)

Anatomic Site	Untreated Controls		Vehicle Controls		Low Dose (11.05 mg/kg)		High Dose (55.24 mg/kg)	
	Males	Females	Males	Females	Males	Females	Males	Females
Endocrine System	0(47-48)	2(45-50)	4(49)	3(42-48)	0(49)	2(37-50)	1(48-49)[c]	2(38-49)
Reproductive System	0(49)	4(50)	1(50)	*(49)	0(48)	6(50)	0(49)	5(49)
Nervous System	none	none	none	none	none	none	none	none
Special Sense Organs	0(49)	0(50)	2(50)	2(49)	1(50)	0(50)	0(50)	4(49)
Musculoskeletal System	none	0(50)	2(50)	2(49)	none	1(50)	none	0(49)
Body Cavities	none	none	none	none	none	none	none	none
All Other Systems	0(49)	none	2(50)	none	0(50)	none	0(50)	none
Tumor Summary:								
Tot. Animals with Primary Tumors	31	26	29	24	35	31	36	42
Tot. Animals with Benign Tumors	11	7	8	7	13	10	14	15
Tot. Animals with Malignant Tumors	26	22	25	20	27	26	28	38
Tot. Animals with Secondary Tumors	3	1	7	0	3	0	2	1
Tot. Animals with Tumors Uncertain Benign or Malignant	0	0	0	0	0	0	0	2

Table 9: Continued

[a]number of tumors for a site or of a particular type for the site.

[b]number of animals examined for the specified anatomic site.

[c]number of animals examined for each tumor type for each site within the system varies between the specified range.

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